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(54) Title: **ANTIBODIES THAT SPECIFICALLY BIND TO GMAD**

(57) Abstract: The present invention relates to antibodies and related molecules that immunospecifically bind to GMAD. Such antibodies have uses, for example, in the prevention and treatment of both insulin- and non insulin-dependent diabetes mellitus (i.e. Type I and Type II diabetes) and other related disorders. The invention also relates to nucleic acid molecules encoding anti-GMAD antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compositions for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially diabetes and other related disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to GMAD.

## **Antibodies that Specifically bind to GMAD**

### **Field of the invention**

[0001] The present invention relates to antibodies and related molecules that immunospecifically bind to GMAD. Such antibodies have uses, for example, in the prevention and treatment of both insulin- and non insulin-dependent diabetes mellitus (i.e. Type I and Type II diabetes) and other related disorders. The invention also relates to nucleic acid molecules encoding anti-GMAD antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compositions for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially diabetes and other related disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to GMAD.

### **Background of the Invention**

[0002] Over the past few decades, an increasing percentage of the population has become diabetic. Diabetes mellitus is categorized into two types: Type I, known as Insulin-Dependent Diabetes Mellitus (IDDM), or Type II, known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM). IDDM is an autoimmune disorder in which the insulin-secreting pancreatic beta cells of the islets of Langerhans are destroyed. In these individuals, recombinant insulin therapy is employed to maintain glucose homeostasis and normal energy metabolism. NIDDM, on the other hand, is a polygenic disorder with no one gene responsible for the progression of the disease.

[0003] In NIDDM, insulin resistance eventually leads to the abolishment of insulin secretion resulting in insulin deficiency. Insulin resistance, at least in part, ensues from a block at the level of glucose uptake and phosphorylation in humans. Diabetics demonstrate a decrease in expression in adipose tissue of insulin-receptor substrate 1 ("IRS1") (Carvalho et al., FASEB J 13(15):2173-8 (1999)), glucose transporter 4 ("GLUT4") (Garvey et al., Diabetes 41(4):465-75 (1992)), and the novel abundant protein M gene transcript 1 ("apM1") (Statnick et al., Int J Exp Diabetes 1(2): 81-8 (2000)), as well as other as of yet unidentified factors. Insulin deficiency in NIDDM leads to failure of normal pancreatic beta-cell function and eventually to pancreatic-beta cell death.



[0004] NIDDM is also characterized by target-tissue resistance to insulin, that cannot be overcome by beta cell hypersecretion. Insulin resistance is accompanied by increased adiposity, which in turn leads to obesity. A polypeptide known as GMAD (also known as Resistin) is specifically secreted by adipocytes, leading to a decrease in insulin action (e.g., glucose transport), and a subsequent increase in adiposity in animal models (Steppan et. al., Nature, vol 409, 18, 307-12 (2001)). In addition, secretion of the GMAD polypeptide has been shown to lead to increased insulin resistance by adipocytes, whereas an inhibition of GMAD leads to an increase in insulin action and thus an increase in cellular glucose uptake (Steppan et. al., Nature, vol 409, 18, 307-12 (2001)).

[0005] Insulin affects fat, muscle, and liver. Insulin is the major regulator of energy metabolism. Malfunctioning of any step(s) in insulin secretion and/or action can lead to many disorders, including for example the dysregulation of oxygen utilization, adipogenesis, glycogenesis, lipogenesis, glucose uptake, protein synthesis, thermogenesis, and maintenance of the basal metabolic rate. This malfunctioning results in diseases and/or disorders that include, but are not limited to, diabetes (e.g., Non-Insulin-Dependent Diabetes Mellitus (NIDDM)), insulin resistance, insulin deficiency, hyperinsulinemia, hyperglycemia, hyperlipidemia, hyperketonemia, dyslipidemia, hypertension, coronary artery disease, renal failure, neuropathy (e.g., autonomic neuropathy, parasympathetic neuropathy, and polyneuropathy), metabolic disorders (e.g., glucose metabolic disorders), endocrine disorders, obesity, weight loss, liver disorders (e.g., liver disease, cirrhosis of the liver, and disorders associated with liver transplant), stroke and conditions associated with these disorders.

[0006] Numerous debilitating diabetes-related secondary effects include, but are not limited to, obesity, forms of blindness (cataracts and diabetic retinopathy), limb amputations, kidney failure, fatty liver, coronary artery disease, stroke and neuropathy. Some of the current drugs used to treat insulin resistance and/or diabetes (e.g., insulin secretagogues such as sulfonylurea, insulin sensitizers such as thiazolidinediones and metformin, and  $\alpha$ -glucosidase and lipase inhibitors) are inadequate due to the dosage amounts and frequency with which they have to be administered as a result of poor pharmacokinetic properties, the lack of effective control over blood sugar levels, and potential side effects, among other reasons. Diabetes therapeutic proteins, in their native state or when recombinantly produced, exhibit a rapid *in vivo* clearance. Typically, significant amounts of therapeutics are required to be effective during therapy. In

addition, small molecules smaller than the 20 kDa range can be readily filtered through the renal tubules (glomerulus) leading to dose-dependent nephrotoxicity.

[0007] The discovery of a new composition that regulates glucose metabolism satisfies a need in the art by providing new compositions which are useful in the diagnosis, treatment, prevention and/or prognosis of diabetes, as well as endocrine disorders, hyperglycemia, liver disorders, inflammation, and aberrant cell growth. Furthermore, the identification of a new composition that regulates glucose metabolism permits the development of a range of derivatives, agonists and antagonists which in turn have applications in the diagnosis, treatment, prevention and/or prognosis of a range of conditions such as diabetes, musculoskeletal disorders, cartilage and bone growth disorders, liver disorders, inflammation, and aberrant cell growth.

#### **Summary of the Invention**

[0008] The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a GMAD polypeptide or polypeptide fragment or variant of a GMAD. In particular, the invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment or variant of human GMAD such as those of SEQ ID NO:2.

[0009] The present invention relates to methods and compositions for preventing, treating or ameliorating a disease or disorder comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that specifically bind to a GMAD polypeptide or a fragment or variant thereof. In specific embodiments, the present invention relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with GMAD function or aberrant GMAD expression, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to a GMAD polypeptide or a fragment or variant thereof. In highly preferred embodiments, the present invention relates to antibody-based methods and compositions for preventing, treating or ameliorating Non-Insulin Dependent Diabetes Mellitus (NIDDM) and/or conditions associated with NIDDM. Other diseases and disorders which can be treated,

prevented or ameliorated with the antibodies of the invention include, but are not limited to, insulin resistance, insulin deficiency, hyperinsulinemia, hyperglycemia, hyperlipidemia, hyperketonemia, dyslipidemia, hypertension, coronary artery disease, renal failure, neuropathy (e.g., autonomic neuropathy, parasympathetic neuropathy, and polyneuropathy), metabolic disorders (e.g., glucose metabolic disorders), endocrine disorders, obesity, weight loss, liver disorders (e.g., liver disease, cirrhosis of the liver, and disorders associated with liver transplant), stroke and conditions associated with these disorders.

[0010] The present invention also encompasses methods and compositions for detecting, diagnosing, or prognosing diseases or disorders comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that specifically bind to GMAD or a fragment or variant thereof. In specific embodiments, the present invention also encompasses methods and compositions for detecting, diagnosing, or prognosing diseases or disorders associated with GMAD function or GMAD receptor function or aberrant GMAD or GMAD receptor expression, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that specifically bind to GMAD or a fragment or variant thereof. In highly preferred embodiments, the present invention relates to antibody-based methods and compositions for detecting, diagnosing, or prognosing Non-Insulin Dependent Diabetes Mellitus (NIDDM) and/or conditions associated with NIDDM. Other diseases and disorders which can be detected, diagnosed, or prognosed with the antibodies of the invention include, but are not limited to, insulin resistance, insulin deficiency, hyperinsulinemia, hyperglycemia, hyperlipidemia, hyperketonemia, dyslipidemia, hypertension, coronary artery disease, renal failure, neuropathy (e.g., autonomic neuropathy, parasympathetic neuropathy, and polyneuropathy), metabolic disorders (e.g., glucose metabolic disorders), endocrine disorders, obesity, weight loss, liver disorders (e.g., liver disease, cirrhosis of the liver, and disorders associated with liver transplant), inflammatory disorders (e.g., asthma, allergic disorders) stroke and proliferative disorders.

[0011] Another embodiment of the present invention includes the use of the antibodies of the invention as a diagnostic tool to monitor the expression of GMAD expression on cells.

[0012] Single chain Fv's (scFvs) that specifically bind GMAD polypeptides (SEQ ID NO:2) have been generated. Thus, the invention encompasses these scFvs, listed in Table 1. In addition, the invention encompasses cell lines engineered to express antibodies corresponding to these scFvs which are deposited with the American Type Culture Collection ("ATCC") as of the dates listed in Table 1 and given the ATCC Deposit Numbers identified in Table 1. The ATCC is located at 10801 University Boulevard, Manassas, VA 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

[0013] Further, the present invention encompasses polynucleotides encoding the scFvs, as well as the amino acid sequences of the scFvs. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of the scFvs referred to in Table 1), that specifically bind to GMAD polypeptides or fragments or variants thereof are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies and/or molecules. In highly preferred embodiments, the present invention encompasses antibodies, or fragments or variants thereof, that bind to the mature form of the GMAD polypeptide (or fragments and variants thereof).

[0014] The present invention also provides anti-GMAD antibodies which are coupled to a detectable label, such as an enzyme, a fluorescent label, a luminescent label, or a bioluminescent label. The present invention also provides anti-GMAD antibodies which are coupled to a therapeutic or cytotoxic agent. The present invention also provides anti-GMAD antibodies which are coupled to a radioactive material.

[0015] The present invention further provides antibodies that inhibit or abolish GMAD activity. In highly preferred embodiments of the present invention, anti-GMAD antibodies of the present invention are used to treat, prevent or ameliorate NIDDM and/or conditions associated with NIDDM. In other highly preferred embodiments, anti-GMAD antibodies of the present invention are administered to an individual alone or in combination with other therapeutic compounds to treat, prevent or ameliorate NIDDM.

[0016] The present invention also provides antibodies that specifically bind one or more GMAD polypeptides and act as either GMAD agonists or GMAD antagonists. In specific embodiments, the antibodies of the invention inhibit the differentiation of GMAD or GMAD receptor expressing cells (e.g., adipocytes). In other specific embodiments, the

antibodies of the invention downregulate or inhibit GMAD expression and thereby promote glucose uptake.

[0017] In further embodiments, the antibodies of the invention have a dissociation constant ( $K_D$ ) of  $10^{-7}$  M or less. In preferred embodiments, the antibodies of the invention have a dissociation constant ( $K_D$ ) of  $10^{-9}$  M or less.

[0018] In further embodiments, antibodies of the invention have an off rate ( $k_{off}$ ) of  $10^{-3}$ /sec or less. In preferred embodiments, antibodies of the invention have an off rate ( $k_{off}$ ) of  $10^{-4}$ /sec or less. In other preferred embodiments, antibodies of the invention have an off rate ( $k_{off}$ ) of  $10^{-5}$ /sec or less.

[0019] The present invention also provides panels of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) wherein the panel members correspond to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs,  $F(ab')_2$  fragments, Fd fragments, disulfide-linked Fvs (sdFvs), anti-idiotypic (anti-Id) antibodies, and scFvs).

[0020] The present invention further provides mixtures of antibodies, wherein the mixture corresponds to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs,  $F(ab')_2$  fragments, Fd fragments, disulfide-linked Fvs (sdFvs), anti-idiotypic (anti-Id) antibodies, and scFvs). The present invention also provides for compositions comprising, or alternatively consisting of, one, two, three, four, five, ten, fifteen, twenty, or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). A composition of the invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty, or more amino acid sequences of one or more antibodies or fragments or variants thereof. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one or more antibodies of the invention.

[0021] The present invention also provides for fusion proteins comprising an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention, and a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain). Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention. A composition of the present invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention. Alternatively, a composition of the

invention may comprise, or alternatively consist of, nucleic acid molecules encoding one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention.

[0022] The present invention also provides for a nucleic acid molecule(s), generally isolated, encoding an antibody (including molecules, such as scFvs, VH domains, or VL domains, that comprise, or alternatively consist of, an antibody fragment or variant thereof) of the invention. The present invention also provides a host cell transformed with a nucleic acid molecule of the invention and progeny thereof. The present invention also provides a method for the production of an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention. The present invention further provides a method of expressing an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention from a nucleic acid molecule. These and other aspects of the invention are described in further detail below.

### **Detailed Description of the Invention**

#### **Definitions**

[0023] The term “antibody,” as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that specifically binds an antigen. As such, the term antibody encompasses not only whole antibody molecules, but also antibody multimers and antibody fragments as well as variants (including derivatives) of antibodies, antibody multimers and antibody fragments. Examples of molecules which are described by the term “antibody” herein include, but are not limited to: single chain Fvs (scFvs), Fab fragments, Fab’ fragments, F(ab’)<sub>2</sub>, disulfide linked Fvs (sdFvs), Fvs, and fragments comprising or alternatively consisting of, either a VL or a VH domain. The term “single chain Fv” or “scFv” as used herein refers to a polypeptide comprising a VL domain of antibody linked to a VH domain of an antibody. Antibodies that specifically bind to GMAD may have cross-reactivity with other antigens. Preferably, antibodies that specifically bind to GMAD do not cross-react with other antigens. Antibodies that specifically bind to GMAD can be identified, for example, by immunoassays or other techniques known to those of skill in the art, *e.g.*, the immunoassays described in the Examples below.

[0024] Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention), intracellularly-made antibodies (*i.e.*, intrabodies), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA<sub>1</sub> and IgA<sub>2</sub>) or subclass of immunoglobulin molecule. Preferably, an antibody of the invention comprises, or alternatively consists of, a VH domain, VH CDR, VL domain, or VL CDR having an amino acid sequence of any one of those referred to in Table 1, or a fragment or variant thereof. In a preferred embodiment, the immunoglobulin is an IgG1 isotype. In another preferred embodiment, the immunoglobulin is an IgG4 isotype. Immunoglobulins may have both a heavy and light chain. An array of IgG, IgE, IgM, IgD, IgA, and IgY heavy chains may be paired with a light chain of the kappa or lambda forms.

[0025] Antibodies of the invention may also include multimeric forms of antibodies. For example, antibodies of the invention may take the form of antibody dimers, trimers, or higher-order multimers of monomeric immunoglobulin molecules. Dimers of whole immunoglobulin molecules or of F(ab')<sub>2</sub> fragments are tetravalent, whereas dimers of Fab fragments or scFv molecules are bivalent. Individual monomers within an antibody multimer may be identical or different, *i.e.*, they may be heteromeric or homomeric antibody multimers. For example, individual antibodies within a multimer may have the same or different binding specificities.

[0026] Multimerization of antibodies may be accomplished through natural aggregation of antibodies or through chemical or recombinant linking techniques known in the art. For example, some percentage of purified antibody preparations (*e.g.*, purified IgG1 molecules) spontaneously form protein aggregates containing antibody homodimers, and other higher-order antibody multimers. Alternatively, antibody homodimers may be formed through chemical linkage techniques known in the art. For example, heterobifunctional crosslinking agents including, but not limited to, SMCC [succinimidyl 4-(maleimidomethyl)cyclohexane-1-carboxylate] and SATA [N-succinimidyl S-acetylthio-acetate] (available, for example, from Pierce Biotechnology, Inc. (Rockford, IL)) can be used to form antibody multimers. An exemplary protocol for the formation of antibody homodimers is given in Ghetie et al., Proceedings of the National Academy of

Sciences USA (1997) 94:7509-7514, which is hereby incorporated by reference in its entirety. Antibody homodimers can be converted to Fab'2 homodimers through digestion with pepsin. Another way to form antibody homodimers is through the use of the autophilic T15 peptide described in Zhao and Kohler, The Journal of Immunology (2002) 25:396-404, which is hereby incorporated by reference in its entirety.

[0027] Alternatively, antibodies can be made to multimerize through recombinant DNA techniques. IgM and IgA naturally form antibody multimers through the interaction with the J chain polypeptide. Non-IgA or non-IgM molecules, such as IgG molecules, can be engineered to contain the J chain interaction domain of IgA or IgM, thereby conferring the ability to form higher order multimers on the non-IgA or non-IgM molecules. (see, for example, Chintalacharuvu et al., (2001) Clinical Immunology 101:21-31. and Frigerio et al., (2000) Plant Physiology 123:1483-94., both of which are hereby incorporated by reference in their entireties.) ScFv dimers can also be formed through recombinant techniques known in the art; an example of the construction of scFv dimers is given in Goel et al., (2000) Cancer Research 60:6964-6971 which is hereby incorporated by reference in its entirety. Antibody multimers may be purified using any suitable method known in the art, including, but not limited to, size exclusion chromatography.

[0028] By "isolated antibody" is intended an antibody removed from its native environment. Thus, an antibody produced by, purified from and/or contained within a hybridoma and/or a recombinant host cell is considered isolated for purposes of the present invention.

[0029] Unless otherwise defined in the specification, specific binding or immunospecific binding by an anti-GMAD antibody means that the anti-GMAD antibody binds GMAD but does not significantly bind to (i.e., cross react with) proteins other than GMAD, such as other proteins in the same family of proteins). An antibody that binds GMAD protein and does not cross-react with other proteins is not necessarily an antibody that does not bind said other proteins in all conditions; rather, the GMAD-specific antibody of the invention preferentially binds GMAD compared to its ability to bind said other proteins such that it will be suitable for use in at least one type of assay or treatment, i.e., give low background levels or result in no unreasonable adverse effects in treatment. It is well known that the portion of a protein bound by an antibody is known as the epitope. An epitope may either be linear (i.e., comprised of sequential amino acids residues in a protein sequences) or conformational (i.e., comprised of one or more amino



acid residues that are not contiguous in the primary structure of the protein but that are brought together by the secondary, tertiary or quaternary structure of a protein). Given that GMAD-specific antibodies bind to epitopes of GMAD, an antibody that specifically binds GMAD may or may not bind fragments of GMAD and/or variants of GMAD (e.g., proteins that are at least 90% identical to GMAD) depending on the presence or absence of the epitope bound by a given GMAD-specific antibody in the GMAD fragment or variant. Likewise, GMAD-specific antibodies of the invention may bind species orthologues of GMAD (including fragments thereof) depending on the presence or absence of the epitope recognized by the antibody in the orthologue. Additionally, GMAD-specific antibodies of the invention may bind modified forms of GMAD, for example, GMAD fusion proteins. In such a case when antibodies of the invention bind GMAD fusion proteins, the antibody must make binding contact with the GMAD moiety of the fusion protein in order for the binding to be specific. Antibodies that specifically bind to GMAD can be identified, for example, by immunoassays or other techniques known to those of skill in the art, e.g., the immunoassays described in the Examples below.

[0030] The term "variant" as used herein refers to a polypeptide that possesses a similar or identical amino acid sequence as a GMAD polypeptide, a fragment of a GMAD polypeptide, an anti-GMAD antibody and/or antibody fragment thereof. A variant having a similar amino acid sequence refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide comprising, or alternatively consisting of, an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the amino acid sequence of a GMAD polypeptide, or a fragment thereof, an anti-GMAD antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those of one or more scFvs referred to in Table 1) described herein; (b) a polypeptide encoded by a nucleotide sequence, the complementary sequence of which hybridizes under stringent conditions to a nucleotide sequence encoding a GMAD polypeptide (e.g., SEQ ID NO:2), a fragment of a GMAD polypeptide, an anti-GMAD antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein, of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino

acid residues, at least 30 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99%, identical to the nucleotide sequence encoding a GMAD polypeptide, a fragment of a GMAD polypeptide, an anti-GMAD antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those of one or more scFvs referred to in Table 1), described herein. Preferably, a variant GMAD polypeptide, a variant fragment of a GMAD polypeptide, or a variant anti-GMAD antibody and/or antibody fragment possess similar or identical function and/or structure as the reference GMAD polypeptide, the reference fragment of a GMAD polypeptide, or the reference anti-GMAD antibody and/or antibody fragment, respectively.

[0031] A polypeptide with similar structure to a GMAD polypeptide, a fragment of a GMAD polypeptide, an anti-GMAD antibody or antibody fragment thereof, described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a GMAD polypeptide, a fragment of a GMAD polypeptide, an anti-GMAD antibody, or antibody fragment thereof, described herein. The structure of a polypeptide can be determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

[0032] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide at the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity =

number of identical overlapping positions/total number of positions x 100%). In one embodiment, the two sequences are the same length.

[0033] The determination of percent identity between two sequences can be accomplished using a mathematical algorithm known to those of skill in the art. An example of a mathematical algorithm for comparing two sequences is the algorithm of Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 87:2264-2268(1990), modified as in Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 90:5873-5877(1993). The BLASTn and BLASTx programs of Altschul, et al. *J. Mol. Biol.* 215:403-410(1990) have incorporated such an algorithm. BLAST nucleotide searches can be performed with the BLASTn program (score = 100, wordlength = 12) to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTx program (score = 50, wordlength = 3) to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. *Nucleic Acids Res.* 25:3589-3402(1997). Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI-BLAST programs, the default parameters of the respective programs (e.g., BLASTx and BLASTn) can be used.

[0034] Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). The ALIGN program (version 2.0) which is part of the GCG sequence alignment software package has incorporated such an algorithm. Other algorithms for sequence analysis known in the art include ADVANCE and ADAM as described in Torellis and Robotti *Comput. Appl. Biosci.*, 10 :3-5(1994); and FASTA described in Pearson and Lipman *Proc. Natl. Acad. Sci.* 85:2444-8(1988). Within FASTA, ktup is a control option that sets the sensitivity and speed of the search.

[0035] The term "derivative" as used herein, refers to a variant polypeptide of the invention that comprises, or alternatively consists of, an amino acid sequence of a GMAD polypeptide, a fragment of a GMAD polypeptide, or an antibody of the invention which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a GMAD polypeptide, a fragment of a GMAD polypeptide, or an antibody that specifically binds to a GMAD polypeptide which has been modified, e.g., by the covalent attachment of any type of

molecule to the polypeptide. For example, but not by way of limitation, a GMAD polypeptide, a fragment of a GMAD polypeptide, or an anti-GMAD antibody, may be modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. A derivative of a GMAD polypeptide, a fragment of a GMAD polypeptide, or an anti-GMAD antibody, may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a GMAD polypeptide, a fragment of a GMAD polypeptide, or an anti-GMAD antibody, may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a GMAD polypeptide, a fragment of a GMAD polypeptide, or an anti-GMAD receptor antibody, described herein.

[0036] The term "fragment" as used herein refers to a polypeptide comprising an amino acid sequence of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 35 amino acid residues, at least 40 amino acid residues, at least 45 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, or at least 100 amino acid residues of the amino acid sequence of GMAD, or an anti-GMAD antibody (including molecules such as scFv's, that comprise, or alternatively consist of, antibody fragments or variants thereof) that specifically binds to GMAD.

[0037] The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[0038] As used herein the phrase "splice variant" refers to cDNA molecules produced from a RNA molecules initially transcribed from the same genomic DNA sequence which have undergone alternative RNA splicing. Alternative RNA splicing occurs when a primary RNA transcript undergoes splicing, generally for the removal of introns, which results in the production of more than one mRNA molecule each of which may encode

different amino acid sequences. The term "splice variant" also refers to the proteins encoded by the above cDNA molecules.

[0039] Unless indicated, "GMAD proteins" and "GMAD polypeptides" refer to all fragments and variants of the protein of SEQ ID NO:2, as well as to proteins resulting from the alternate splicing of the genomic DNA sequences encoding proteins having regions of amino acid sequence identity and GMAD activity which correspond to the protein of SEQ ID NO:2 as well as GMAD allelic variants.

### Antibody Structure

[0040] The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. *See generally, Fundamental Immunology* Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site.

[0041] Thus, an intact IgG antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are the same.

[0042] The chains all exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper variable regions, also called complementarity determining regions or CDRs. The CDRs from the heavy and the light chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk *J Mol. Biol.* 196:901-917 (1987); Chothia et al. *Nature* 342:878-883 (1989).

[0043] A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. *See, e.g.,* Songsivilai & Lachmann *Clin. Exp. Immunol.* 79: 315-321 (1990), Kostelny et al. *J Immunol.* 148:1547-1553 (1992). In addition, bispecific antibodies may be formed as "diabodies" (Holliger et al. "Diabodies: small bivalent and bispecific antibody fragments" *PNAS USA* 90:6444-6448 (1993)) or "Janusins" (Traunecker et al. "Bispecific single chain molecules (Janusins) target cytotoxic lymphocytes on HIV infected cells" *EMBO J* 10:3655-3659 (1991) and Traunecker et al. "Janusin: new molecular design for bispecific reagents" *Int J Cancer Suppl* 7:51-52 (1992)).

[0044] Production of bispecific antibodies can be a relatively labor intensive process compared with production of conventional antibodies and yields and degree of purity are generally lower for bispecific antibodies. Bispecific antibodies do not exist in the form of fragments having a single binding site (e.g., Fab, Fab', and Fv).

#### Anti-GMAD Antibodies

[0045] Using phage display technology, single chain antibody molecules ("scFvs") that immunospecifically bind to GMAD polypeptides (or fragments or variants thereof) have been identified. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind to one or more GMAD polypeptides (or fragments or variants thereof) are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[0046] In particular, the invention also relates to scFvs comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of SEQ ID NOS: 40-136 as referred to in Table 1 below. scFvs corresponding to SEQ ID NO:40-136 were selected for their ability to specifically bind GMAD polypeptide. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that specifically bind to one or more GMAD polypeptide are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules (e.g., SEQ ID NOS: 137-233).

[0047] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a GMAD polypeptide or a polypeptide fragment or variants of GMAD. In particular, the invention provides antibodies corresponding to the scFvs referred to in Table 1, such scFvs may routinely be "converted" to immunoglobulin molecules by inserting, for example, the nucleotide sequences encoding the VH and/or VL domains of the scFv into an expression vector containing the constant domain sequences and engineered to direct the expression of the immunoglobulin molecule, as described in more detail in Example 2 below.

[0048] NS0 cell lines that express IgG1 antibodies that comprise the VH and VL domains of scFvs of the invention have been deposited with the American Type Culture Collection ("ATCC") on the dates listed in Table 1 and given the ATCC Deposit Numbers identified in Table 1. The ATCC is located at 10801 University Boulevard, Manassas, VA 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for Purposes of Patent Procedure.

[0049] Accordingly, in one embodiment, the invention provides antibodies that comprise the VH and VL domains of scFvs of the invention.

Table 1

scFv	scFv protein SEQ ID NO:	scFv DNA SEQ ID NO:	AAs of VH Domain	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	AAs of VL Domain	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	Cell Line Expressing antibody	ATCC Deposit Number	ATCC Deposit Date
GMBC603	40	137	1-123	31-35	50-66	99-112	139-249	161-174	190-196	229-238			
GMBC604	41	138	1-117	31-35	50-66	99-106	133-243	155-168	184-190	223-232			
GMBC605	42	139	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236			
GMBC606	43	140	1-119	31-35	50-66	99-108	135-242	156-166	182-188	221-231			
GMBC607	44	141	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236			
GMBC608	45	142	1-123	31-35	50-66	99-112	139-246	160-170	186-192	225-235			
GMBC609	46	143	1-121	31-35	50-68	101-110	137-247	159-171	187-193	226-236			
GMBC610	47	144	1-118	31-35	50-66	99-107	134-241	155-165	181-187	220-230			
GMBC612	48	145	1-116	31-35	50-66	99-105	132-239	155-165	181-187	220-229			
GMBC613	49	146	1-122	31-35	50-66	99-111	138-245	159-169	185-191	224-234			
GMBC614	50	147	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236			
GMBC615	51	148	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236			
GMBC616	52	149	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236			
GMBC617	53	150	1-117	31-35	50-65	98-106	133-243	155-168	184-190	223-232			
GMBC618	54	151	1-121	31-35	50-68	101-110	137-247	159-171	187-193	226-236			
GMBC619	55	152	1-121	31-35	50-66	99-110	137-244	158-168	184-190	223-233			
GMBC620	56	153	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236			
GMBC621	57	154	1-118	31-35	50-66	99-107	134-241	155-165	181-187	220-230			
GMBC625	58	155	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236			
GMBC626	59	156	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236			
GMBC627	60	157	1-118	31-35	50-66	99-107	134-244	156-169	185-191	224-233			



GMBC628	61	158	1-126	31-35	50-66	99-115	142-249	163-173	189-195	228-238		
GMBC629	62	159	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC630	63	160	1-119	31-35	50-66	99-108	135-242	156-166	182-188	221-231		
GMBC632	64	161	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC634	65	162	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC635	66	163	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC638	67	164	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC639	68	165	1-130	31-35	50-66	99-119	146-253	167-177	193-199	232-242		
GMBC641	69	166	1-120	31-35	50-66	99-109	136-243	157-167	183-189	222-232		
GMBC642	70	167	1-120	31-35	50-66	99-109	136-243	157-167	183-189	222-232		
GMBC645	71	168	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC646	72	169	1-118	31-35	50-66	99-107	134-241	157-167	183-189	222-231		
GMBC647	73	170	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC648	74	171	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC649	75	172	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC651	76	173	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC652	77	174	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC653	78	175	1-119	31-35	50-66	99-108	135-246	157-169	185-191	224-235		
GMBC654	79	176	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC655	80	177	1-116	31-35	50-66	99-105	132-239	155-165	181-187	220-229		
GMBC657	81	178	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC658	82	179	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC659	83	180	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC660	84	181	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC662	85	182	1-117	31-35	50-66	99-106	133-243	155-168	184-190	223-232		
GMBC664	86	183	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC665	87	184	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC666	88	185	1-121	31-35	50-68	101-110	137-247	159-171	187-193	226-236		

GMBC667	89	186	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC668	90	187	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC669	91	188	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC670	92	189	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC672	93	190	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC673	94	191	1-122	31-35	50-66	99-111	138-243	159-169	185-191	224-232		
GMBC676	95	192	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC678	96	193	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC679	97	194	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC681	98	195	1-117	31-35	50-66	99-106	133-240	156-166	182-188	221-230		
GMBC682	99	196	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC683	100	197	1-118	31-35	50-66	99-107	134-241	155-165	181-187	220-230		
GMBC684	101	198	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC685	102	199	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC686	103	200	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC687	104	201	1-124	31-35	50-66	99-113	140-247	163-173	189-195	228-237		
GMBC689	105	202	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC690	106	203	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC691	107	204	1-130	31-35	50-66	99-119	146-253	167-177	193-199	232-242		
GMBC692	108	205	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC693	109	206	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC696	110	207	1-118	31-35	50-66	99-107	134-241	155-165	181-187	220-230		
GMBC725	111	208	1-119	31-35	50-66	99-108	135-242	156-166	182-188	221-231		
GMBC727	112	209	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMBC729	113	210	1-121	31-35	50-68	101-110	137-244	158-168	184-190	223-233		
GMBC730	114	211	1-121	31-35	50-68	101-110	137-247	159-172	188-194	227-236		
GMCC101	115	212	1-118	31-35	50-66	99-107	134-245	157-169	185-191	224-234		
GMCC102	116	213	1-133	31-35	50-66	99-122	149-260	172-184	200-206	239-249		

GMCC105	117	214	1-123	31-35	50-66	99-112	139-250	163-173	189-195	228-239		
GMCC106	118	215	1-118	31-36	51-66	99-107	134-245	157-169	185-191	224-234		
GMCC107	119	216	1-122	31-35	50-66	99-111	138-250	161-174	190-196	229-239		
GMCC108	120	217	1-128	31-35	50-66	99-117	144-255	167-177	193-199	232-244		
GMCC109	121	218	1-122	31-35	50-66	99-111	138-244	161-171	187-193	226-233		
GMCC110	122	219	1-125	31-37	52-67	100-114	141-250	165-175	191-197	230-239		
GMCC112	123	220	1-120	31-35	50-65	98-109	136-245	161-172	188-194	227-235		
GMCC114	124	221	1-124	31-36	51-67	100-113	140-250	164-174	190-196	229-239		
GMCC118	125	222	1-127	31-35	50-68	101-116	143-251	166-176	192-198	231-240		
GMCC119	126	223	1-125	31-35	50-66	99-114	141-252	164-177	193-199	232-241		
GMCC124	127	224	1-124	31-35	50-66	99-113	140-251	163-175	191-197	230-240		
GMCC125	128	225	1-120	31-35	50-66	99-109	136-247	160-170	186-192	225-236		
GMCC126	129	226	1-123	31-36	51-66	99-112	139-246	162-172	188-194	227-235		
GMCC127	130	227	1-116	31-35	50-66	99-105	132-242	156-166	182-188	221-231		
GMCC129	131	228	1-119	31-35	50-66	99-108	135-246	159-169	185-191	224-235		
GMCC131	132	229	1-120	31-35	50-65	98-109	136-248	159-172	188-194	227-237		
GMCC136	133	230	1-120	31-35	50-66	99-109	136-245	161-171	187-193	226-235		
GMCC138	134	231	1-122	31-37	52-67	100-111	138-248	162-172	188-194	227-237		
GMCC142	135	232	1-121	31-35	50-66	99-110	137-246	161-171	187-193	226-235		
GMCC151	136	233	1-123	31-35	50-66	99-112	139-250	163-173	189-195	228-239		

[0050] The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to a GMAD polypeptide or a fragment, variant, or fusion protein thereof. A GMAD polypeptide includes, but is not limited to, GMAD (SEQ ID NO:2) or the polypeptide encoded by the GMAD cDNA contained in ATCC Deposit No. 209215 on August 21, 1997. GMAD may be produced through recombinant expression of nucleic acids encoding the polypeptide of SEQ ID NO:2 (e.g., the GMAD cDNA in the ATCC Deposit Number 209215). Antibodies of the invention may specifically bind GMAD as well as fragments and variants thereof, and are described in more detail below.

#### **GMAD Polypeptides**

[0051] In certain embodiments of the present invention, the antibodies of the present invention bind GMAD polypeptide, or fragments or variants thereof. The following section describes the GMAD polypeptides, fragments and variants that the antibodies of the invention may bind in more detail.

[0052] In certain embodiments, the antibodies of the present invention specifically bind GMAD polypeptide. An antibody that specifically binds GMAD may, in some embodiments, bind fragments, variants (including species orthologs and allelic variants of GMAD), multimers or modified forms of GMAD. For example, an antibody specific for GMAD may bind the GMAD moiety of a fusion protein comprising all or a portion of GMAD.

[0053] GMAD proteins may be found as homodimers. Accordingly, the present invention relates to antibodies that bind GMAD proteins found as homodimers. In specific embodiments, antibodies of the invention bind GMAD homodimers.

[0054] GMAD proteins may also be found as monomers or multimers (i.e., dimers, trimers, tetramers, and higher multimers). Accordingly, the present invention relates to antibodies that bind GMAD proteins found as monomers or as part of multimers. In specific embodiments, antibodies of the invention bind GMAD monomers, dimers, trimers or tetramers. In additional embodiments, antibodies of the invention bind at least dimers, at least trimers, or at least tetramers containing one or more GMAD polypeptides.

[0055] Antibodies of the invention may bind GMAD homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only GMAD proteins of

the invention (including GMAD fragments, variants, and fusion proteins, as described herein). These homomers may contain GMAD proteins having identical or different polypeptide sequences. In a specific embodiment, a homomer of the invention is a multimer containing only GMAD proteins having an identical polypeptide sequence. In another specific embodiment, antibodies of the invention bind GMAD homomers containing GMAD proteins having different polypeptide sequences. In specific embodiments, antibodies of the invention bind a GMAD homodimer (e.g., containing GMAD proteins having identical or different polypeptide sequences) or a homotrimer (e.g., containing GMAD proteins having identical or different polypeptide sequences). In additional embodiments, antibodies of the invention bind at least a homodimer, at least a homotrimer, or at least a homotetramer of GMAD.

[0056] As used herein, the term heteromer refers to a multimer containing heterologous proteins (i.e., proteins containing polypeptide sequences that do not correspond to GMAD polypeptide sequences) in addition to the GMAD proteins of the invention. In a specific embodiment, antibodies of the invention bind a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the antibodies of the invention bind at least a homodimer, at least a homotrimer, or at least a homotetramer containing one or more GMAD polypeptides.

[0057] Antibodies of the invention may bind GMAD protein multimers that are the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, antibodies of the invention may bind multimers, such as, for example, homodimers or homotrimers, that are formed when GMAD proteins contact one another in solution. In another embodiment, antibodies of the invention may bind heteromultimers, such as, for example, heterotrimers or heterotetramers, that are formed when proteins of the invention contact antibodies to GMAD polypeptides (or antibodies to the heterologous polypeptide sequence in a fusion protein) in solution. In other embodiments, multimers that one or more antibodies of the invention may bind are formed by covalent associations with and/or between the GMAD proteins of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence of the protein (e.g., the polypeptide sequence recited in SEQ ID NO:2 or the polypeptide encoded by the deposited GMAD cDNA clone of ATCC Deposit 209215). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide

sequences of the proteins which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a GMAD fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a GMAD-Fc fusion protein (as described herein). In another specific example, covalent associations of fusion proteins are between heterologous polypeptide sequences from another GMAD-related polypeptides (e.g., other FIZZ, RELM family) that are capable of forming covalently associated multimers, such as for example, ositeoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety).

[0058] Antibodies of the invention may bind GMAD protein multimers that were generated using chemical techniques known in the art. For example, proteins desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers that may be bound by one or more antibodies of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the polypeptide sequence of the proteins desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, proteins that may be bound by one or more antibodies of the invention may be routinely modified by the addition of cysteine or biotin to the C terminus or N-terminus of the polypeptide sequence of the protein and techniques known in the art may be applied to generate multimers containing one or more of these modified proteins (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the protein components desired to be contained in the multimer that one or more antibodies of the invention may bind (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[0059] Alternatively, antibodies of the invention may bind GMAD protein multimers that were generated using genetic engineering techniques known in the art. In one embodiment, proteins contained in multimers that may be bound by one or more antibodies of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer that may be bound by one or more antibodies of the invention are generated by ligating a polynucleotide sequence encoding a GMAD polypeptide to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant GMAD polypeptides which contain a transmembrane domain and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, two or more GMAD polypeptides are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple GMAD polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology. In specific embodiments, antibodies of the invention bind proteins comprising multiple GMAD polypeptides separated by peptide linkers.

[0060] Another method for preparing multimer GMAD polypeptides involves use of GMAD polypeptides fused to a leucine zipper or isoleucine polypeptide sequence. Leucine zipper domains and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric GMAD proteins are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a soluble GMAD polypeptide fused to

a peptide that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric GMAD is recovered from the culture supernatant using techniques known in the art. In specific embodiments, antibodies of the invention bind GMAD-leucine zipper fusion protein monomers and/or GMAD-leucine zipper fusion protein multimers.

[0061] Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric GMAD. In specific embodiments, antibodies of the invention bind GMAD-fusion protein monomers and/or GMAD fusion protein trimers.

[0062] Antibodies that bind GMAD polypeptides may bind them as isolated polypeptides or in their naturally occurring state. For, example antibodies of the present invention may bind recombinantly produced GMAD polypeptides. In a specific embodiment, antibodies of the present invention bind a GMAD polypeptide purified from a cell culture wherein cells in said cell culture comprise a polynucleotide encoding amino acids 1 to 108 of SEQ ID NO:2 operably associated with a regulatory sequence that controls expression of said polynucleotide. Antibodies of the present invention may bind GMAD polypeptide fragments comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:2, encoded by the GMAD cDNA contained in ATCC Deposit Number 209215, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the GMAD nucleotide sequence contained in ATCC Deposit Number 209215, or the complementary strand thereto. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Antibodies of the present invention may bind polypeptide fragments, including, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 23, 24 to 43, 44 to 63, 64 to 83 and/or 84 to 108, of SEQ ID NO:2. In this context "about" includes the particularly recited value, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Moreover, polypeptide fragments that antibodies of the invention may bind can be at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 amino acids in length. In this context "about" includes the particularly recited value, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

[0063] Preferably, antibodies of the present invention bind polypeptide fragments selected from the group: a polypeptide comprising or alternatively, consisting of, a fragment of the predicted mature GMAD polypeptide, wherein the fragment has a GMAD



functional activity (e.g., antigenic activity or biological activity); or a polypeptide comprising, or alternatively, consisting of, one, two, three, four or more, epitope bearing portions of the GMAD protein. The amino acid residues constituting the preferred epitopes have been predicted by computer analysis. Thus, as one of ordinary skill would appreciate, the amino acid residues constituting these domains may vary slightly (e.g., by about 1 to about 15 amino acid residues) depending on the criteria used to define each epitope. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0064] In another preferred embodiment, antibodies of the present invention bind GMAD polypeptides comprising, or alternatively consisting of, the expressed and/or mature polypeptide of GMAD (amino acid residues 21-108 of SEQ ID NO:2). In highly preferred embodiments, the antibodies of the invention that bind all or a portion of the mature GMAD polypeptide and inhibit GMAD-induced insulin resistance (i.e. gradual reduction in insulin uptake) in cells expressing GMAD (e.g., adipocytes). In other highly preferred embodiments, the antibodies of the invention that bind all or a portion of the mature GMAD polypeptide and inhibit GMAD-induced glucose resistance (i.e. gradual reduction in insulin-mediated glucose uptake) in cells expressing GMAD (e.g., adipocytes).

[0065] Antibodies of the invention may also bind fragments comprising, or alternatively, consisting of, structural or functional attributes of GMAD. Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of complete (i.e., full-length) GMAD. Certain preferred regions are those set out in Table 2 and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted in (SEQ ID NO:2), such preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle predicted hydrophilic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming

regions; and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these computer programs.

[0066] The data representing the structural or functional attributes of GMAD set forth in Table 2, as described above, was generated using the various modules and algorithms of the DNA\*STAR set on default parameters. Column I represents the results of a Garnier-Robson analysis of alpha helical regions; Column II represents the results of a Chou-Fasman analysis of alpha helical regions; Column III represents the results of a Garnier Robson analysis of beta sheet regions; Column IV represents the results of a Chou-Fasman analysis of beta sheet regions; Column V represents the results of a Garnier Robson analysis of turn regions; Column VI represents the results of a Chou-Fasman analysis of turn regions; Column VII represents the results of a Garnier Robson analysis of coil regions; Column VIII represents a Kyte-Doolittle hydrophilicity plot; Column; Column IX represents a Hopp-Woods hydrophobicity plot; Column X represents the results of an Eisenberg analysis of alpha amphipathic regions; Column XI represents the results of an Eisenberg analysis of beta amphipathic regions; Column XII represents the results of a Karplus-Schultz analysis of flexible regions; Column XIII represents the Jameson-Wolf antigenic index score; and Column XIV represents the Emini surface probability plot.

[0067] In a preferred embodiment, the data presented in columns VIII, XIII, and XIV of Table 2 can be used to determine regions of GMAD which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0068] The above-mentioned preferred regions set out in Table 2 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in SEQ ID NO:2. As set out in Table 2, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions. Among preferred polypeptide fragments that one or more antibodies of the invention may bind are

those that comprise regions of GMAD that combine several structural features, such as several (e.g., 1, 2, 3, or 4) of the same or different region features set out above and in Table 2.

Table 2

Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met 1	A	A	.	.	.	.	.	-0.68	0.09	.	.	.	-0.30	0.62
Lys 2	A	A	.	.	.	.	.	-1.10	0.23	.	.	.	-0.30	0.26
Ala 3	A	A	.	.	.	.	.	-1.52	0.49	*	.	.	-0.60	0.17
Leu 4	A	A	.	.	.	.	.	-1.94	0.74	.	.	.	-0.60	0.14
Cys 5	A	A	.	.	.	.	.	-2.37	0.81	.	.	.	-0.60	0.06
Leu 6	A	A	.	.	.	.	.	-1.98	1.50	*	.	.	-0.60	0.05
Leu 7	.	A	B	.	.	.	.	-2.88	1.43	.	.	.	-0.60	0.09
Leu 8	.	A	B	.	.	.	.	-3.10	1.39	.	.	.	-0.60	0.12
Leu 9	.	A	B	.	.	.	.	-2.63	1.50	.	.	.	-0.60	0.12
Pro 10	.	A	B	.	.	.	.	-2.78	1.24	.	.	.	-0.60	0.15
Val 11	.	A	B	.	.	.	.	-2.78	1.24	.	.	.	-0.60	0.15
Leu 12	.	A	B	.	.	.	.	-2.82	1.24	.	.	.	-0.60	0.15
Gly 13	.	A	B	.	.	.	.	-2.31	1.20	.	.	.	-0.60	0.07
Leu 14	.	A	B	.	.	.	.	-1.80	1.16	.	.	.	-0.60	0.13
Leu 15	.	A	B	.	.	.	.	-1.54	0.90	.	.	.	-0.60	0.21
Val 16	.	.	B	.	.	T	.	-1.00	0.21	.	.	.	0.10	0.42
Ser 17	.	.	B	.	.	T	.	-1.00	0.27	.	.	F	0.25	0.73
Ser 18	A	.	.	.	.	T	.	-1.32	0.27	.	.	F	0.25	0.73
Lys 19	A	.	.	.	.	T	.	-0.81	0.16	.	.	F	0.25	0.53
Thr 20	A	.	.	B	.	.	.	-0.60	-0.10	.	.	F	0.45	0.53
Leu 21	A	.	.	B	.	.	.	0.26	0.13	.	.	.	-0.30	0.39
Cys 22	A	.	.	B	.	.	.	0.56	-0.26	*	.	.	0.30	0.34

Table 2 (continued)

Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ser 23	A	.	.	B	.	.	.	0.27	-0.26	*	.	.	0.30	0.40
Met 24	A	A	.	.	.	.	.	-0.67	-0.24	*	.	.	0.30	0.49
Glu 25	A	A	.	.	.	.	.	-0.36	-0.24	*	.	.	0.30	0.65
Glu 26	A	A	.	.	.	.	.	0.46	-0.41	.	*	.	0.30	0.77
Ala 27	A	A	.	.	.	.	.	1.23	-0.80	.	*	.	0.75	1.36
Ile 28	A	A	.	.	.	.	.	0.64	-1.41	*	*	.	0.75	1.53
Asn 29	A	A	.	.	.	.	.	1.24	-0.73	*	*	.	0.60	0.62
Glu 30	A	A	.	.	.	.	.	1.24	-0.33	*	*	F	0.60	1.06
Arg 31	A	A	.	.	.	.	.	0.39	-0.83	*	*	F	0.90	2.63
Ile 32	A	A	.	.	.	.	.	0.39	-0.87	*	*	F	0.90	1.21
Gln 33	A	A	.	.	.	.	.	0.93	-0.77	*	*	F	0.75	0.71
Glu 34	A	A	.	.	.	.	.	0.63	-0.34	*	*	.	0.30	0.36
Val 35	A	A	.	.	.	.	.	-0.18	0.04	*	.	.	-0.30	0.68
Ala 36	A	A	.	.	.	.	.	-1.18	0.04	*	*	.	-0.30	0.33
Gly 37	A	A	.	B	.	.	.	-0.99	0.33	*	*	.	-0.30	0.13
Ser 38	A	A	.	B	.	.	.	-0.88	1.11	*	*	.	-0.60	0.15
Leu 39	A	A	.	B	.	.	.	-1.47	0.47	*	*	.	-0.60	0.30
Ile 40	.	A	B	B	.	.	.	-1.50	0.47	*	*	.	-0.60	0.30
Phe 41	.	A	B	B	.	.	.	-1.21	0.73	*	.	.	-0.60	0.16
Arg 42	.	A	B	B	.	.	.	-1.17	0.73	*	*	.	-0.60	0.26
Ala 43	.	A	B	B	.	.	.	-1.76	0.43	*	*	.	-0.60	0.49
Ile 44	.	A	B	B	.	.	.	-1.29	0.43	*	*	.	-0.60	0.40
Ser 45	.	A	B	B	.	.	.	-0.29	0.07	*	.	.	-0.30	0.20
Ser 46	.	.	.	B	.	.	C	0.07	0.07	*	*	F	0.05	0.39
Ile 47	.	.	.	B	.	.	C	-0.34	0.00	*	.	F	0.05	0.55
Gly 48	.	.	.	.	.	T	C	0.24	-0.30	*	.	F	1.05	0.55
Arg 49	.	.	.	.	.	T	C	0.83	-0.69	*	*	F	1.35	0.72

Table 2 (continued)

Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly 50	.	.	.	.	.	T	C	0.28	-0.69	*	.	F	1.50	1.37
Ser 51	.	.	.	.	.	T	C	0.27	-0.73	*	.	F	1.50	1.03
Glu 52	.	.	B	B	.	.	.	0.86	-0.67	*	*	F	1.09	0.76
Ser 53	.	.	B	B	.	.	.	1.31	-0.29	*	*	F	1.28	1.02
Val 54	.	.	B	B	.	.	.	0.86	-0.71	*	*	F	1.92	1.50
Thr 55	.	.	B	B	.	.	.	1.20	-0.67	.	*	F	2.11	0.85
Ser 56	.	.	.	.	T	T	.	0.69	-0.67	.	*	F	3.40	1.07
Arg 57	.	.	.	.	T	T	.	0.10	-0.37	.	*	F	2.76	1.18
Gly 58	.	.	.	.	T	T	.	0.09	-0.51	.	*	F	2.57	0.83
Asp 59	.	.	.	.	T	T	.	0.28	-0.51	.	*	F	2.23	0.89
Leu 60	.	.	B	.	.	.	.	0.38	-0.33	.	*	F	0.99	0.24
Ala 61	.	.	B	.	.	.	.	0.79	0.10	.	*	.	-0.10	0.38
Thr 62	.	.	B	.	.	.	.	0.33	-0.33	*	*	.	0.50	0.45
Cys 63	.	.	B	.	.	T	.	-0.02	0.10	*	*	.	0.10	0.54
Pro 64	.	.	.	.	T	T	.	-0.61	0.20	*	.	F	0.65	0.46
Arg 65	.	.	.	.	T	T	.	-0.66	0.20	*	.	F	0.65	0.32
Gly 66	.	.	.	.	T	T	.	-0.38	0.36	.	.	.	0.50	0.45
Phe 67	.	.	B	B	.	.	.	-0.41	0.27	.	.	.	-0.30	0.42
Ala 68	.	.	B	B	.	.	.	-0.41	0.27	.	.	.	-0.30	0.21
Val 69	.	.	B	B	.	.	.	-0.51	0.84	.	.	.	-0.60	0.11
Thr 70	.	.	B	B	.	.	.	-1.29	0.90	.	.	.	-0.60	0.19
Gly 71	.	.	B	B	.	.	.	-1.29	0.69	.	.	.	-0.60	0.10
Cys 72	.	.	.	.	T	T	.	-0.89	0.61	.	.	.	0.20	0.13
Thr 73	.	.	.	.	T	T	.	-0.89	0.36	.	.	.	0.50	0.12
Cys 74	.	.	.	.	T	T	.	-0.70	0.37	.	.	.	0.50	0.13
Gly 75	.	.	.	.	T	T	.	-0.73	0.51	.	.	.	0.20	0.13
Ser 76	.	.	.	.	T	.	.	-0.69	0.37	.	.	.	0.30	0.09

Table 2 (continued)

Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala 77	.	.	.	.	T	.	.	-0.31	0.27	.	.	.	0.30	0.22
Cys 78	.	.	.	.	T	T	.	0.00	0.61	.	*	.	0.20	0.23
Gly 79	.	.	.	.	T	T	.	-0.19	0.19	.	*	.	0.50	0.29
Ser 80	.	.	.	.	T	T	.	0.27	0.44	.	*	.	0.20	0.21
Trp 81	.	.	B	.	.	T	.	-0.02	-0.06	.	*	.	0.70	0.78
Asp 82	.	A	B	B	.	.	.	0.57	-0.13	.	*	.	0.30	0.79
Val 83	A	A	.	B	.	.	.	0.92	-0.56	.	*	.	0.75	1.02
Arg 84	A	A	.	B	.	.	.	0.96	-0.46	.	*	.	0.45	1.41
Ala 85	A	A	.	.	.	.	.	0.59	-0.89	.	*	F	0.90	1.21
Glu 86	.	A	.	.	T	.	.	0.84	-0.31	.	*	F	0.85	0.88
Thr 87	.	A	.	.	T	.	.	0.18	-0.46	.	*	F	0.85	0.61
Thr 88	.	A	.	.	T	.	.	1.03	0.11	.	*	.	0.10	0.32
Cys 89	.	.	.	.	T	T	.	0.26	0.01	.	*	.	0.50	0.32
His 90	.	.	.	.	T	T	.	0.26	0.59	.	.	.	0.20	0.12
Cys 91	.	.	B	.	.	T	.	-0.09	0.60	.	.	.	-0.20	0.08
Gln 92	.	.	B	.	.	T	.	-0.38	0.54	.	.	.	-0.20	0.16
Cys 93	.	.	.	.	T	.	.	-0.07	0.59	.	.	.	0.00	0.11
Ala 94	.	.	.	.	T	.	.	0.31	0.09	.	.	.	0.30	0.35
Gly 95	.	.	.	.	T	T	.	0.03	0.43	.	.	.	0.20	0.21
Met 96	.	.	.	.	T	T	.	0.36	0.51	.	.	.	0.42	0.57
Asp 97	.	.	.	.	T	T	.	-0.23	0.37	.	.	.	0.94	0.56
Trp 98	.	.	.	.	T	T	.	0.54	0.37	.	.	.	1.16	0.57
Thr 99	.	.	.	.	T	.	.	0.47	-0.06	.	.	.	1.93	1.14
Gly 100	.	.	.	.	T	T	.	0.14	-0.10	*	.	.	2.20	0.37
Ala 101	.	.	.	.	T	T	.	0.86	0.47	*	.	.	1.08	0.19
Arg 102	.	.	.	.	T	T	.	0.00	-0.44	.	.	.	1.76	0.25
Cys 103	.	.	.	.	T	T	.	0.29	-0.29	.	.	.	1.54	0.19

Table 2 (continued)

Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Cys 104	.	.	.	.	T	.	.	0.39	-0.31	*	.	.	1.12	0.32
Arg 105	.	.	B	.	.	.	.	0.34	-0.39	*	.	.	0.50	0.26
Val 106	.	.	B	.	.	.	.	0.54	0.04	*	.	.	-0.10	0.61
Gln 107	.	.	B	.	.	.	.	0.04	-0.10	*	.	.	0.65	1.46
Pro 108	.	.	B	.	.	.	.	0.32	-0.24	.	*	.	0.50	0.95



[0069] In another aspect, the invention provides an antibody that binds a peptide or polypeptide comprising an epitope-bearing portion of a polypeptide described herein. The epitope of this polypeptide portion is an immunogenic or antigenic epitope of a polypeptide of the invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. See, for instance, Geysen *et al.*, *Proc. Natl. Acad. Sci. USA* 81:3998- 4002 (1983).

[0070] As to the selection of peptides or polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G., Shinnick, T. M., Green, N. and Learner, R.A. (1983) Antibodies that react with predetermined sites on proteins. *Science* 219:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins nor to the amino or carboxyl terminals.

[0071] Antigenic epitope-bearing peptides and polypeptides are therefore useful to raise antibodies, including monoclonal antibodies, that bind to a GMAD polypeptide of the invention. See, for instance, Wilson *et al.*, *Cell* 37:767-778 (1984) at 777. Antigenic epitope-bearing peptides and polypeptides preferably contain a sequence of at least seven, more preferably at least nine and most preferably between at least about 15 to about 30 amino acids contained within the amino acid sequence of SEQ ID NO:2.

[0072] Antibodies of the invention may bind one or more antigenic GMAD polypeptides or peptides including, but not limited to: a polypeptide comprising amino acid residues from about 54 to about 59 of SEQ ID NO:2. In this context "about" includes the particularly recited range, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either terminus or at both termini. As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the GMAD protein. Epitope-bearing GMAD peptides and polypeptides may be produced by any conventional means. Houghten, R.A., "General method for the rapid solid-phase synthesis of large

numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids," *Proc. Natl. Acad. Sci. USA* 82:5131-5135 (1985). This "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U.S. Patent No. 4,631,211 to Houghten *et al.* (1986).

[0073] As one of skill in the art will appreciate, GMAD polypeptides and the epitope-bearing fragments thereof described herein can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life *in vivo*. This has been shown, e.g., for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins (EPA 394,827; Traunecker *et al.*, *Nature* 331:84- 86 (1988)). Fusion proteins that have a disulfide-linked dimeric structure due to the IgG part can also be more efficient in binding and neutralizing other molecules than the monomeric GMAD protein or protein fragment alone (Fountoulakis *et al.*, *J Biochem* 270:3958-3964 (1995)). Thus, antibodies of the invention may bind fusion proteins that comprise all or a portion of a GMAD polypeptide.

[0074] Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or "muteins" including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. Antibodies of the present invention may also bind such modified GMAD polypeptides or GMAD polypeptide fragments or variants.

[0075] For instance, for many proteins, including the extracellular domain of a membrane associated protein or the mature form(s) of a secreted protein, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function, or loss of the ability to be bound by a specific antibody. For instance, Ron *et al.*, *J. Biol. Chem.*, 268:2984-2988 (1993) reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 amino-terminal amino acid residues were missing.

[0076] However, even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein,

other functional activities (e.g., biological activities, ability to multimerize, ability to reduce insulin and/or cellular glucose uptake) may still be retained. For example, the ability of shortened GMAD polypeptides to induce and/or bind to antibodies which recognize the complete or mature forms of the GMAD polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a GMAD polypeptide with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six GMAD amino acid residues may often evoke an immune response.

[0077] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the GMAD amino acid sequence of SEQ ID NO:2 up to the arginine residue at position number 102 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues  $n^1$ -108 of SEQ ID NO:2, where  $n^1$  is an integer from 2 to 103 corresponding to the position of the amino acid residue in SEQ ID NO:2.

[0078] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues of K-2 to P-108; A-3 to P-108; L-4 to P-108; C-5 to P-108; L-6 to P-108; L-7 to P-108; L-8 to P-108; L-9 to P-108; P-10 to P-108; V-11 to P-108; L-12 to P-108; G-13 to P-108; L-14 to P-108; L-15 to P-108; V-16 to P-108; S-17 to P-108; S-18 to P-108; K-19 to P-108; T-20 to P-108; L-21 to P-108; C-22 to P-108; S-23 to P-108; M-24 to P-108; E-25 to P-108; E-26 to P-108; A-27 to P-108; I-28 to P-108; N-29 to P-108; E-30 to P-108; R-31 to P-108; I-32 to P-108; Q-33 to P-108; E-34 to P-108; V-35 to P-108; A-36 to P-108; G-37 to P-108; S-38 to P-108; L-39 to P-108; I-40 to P-108; F-41 to P-108; R-42 to P-108; A-43 to P-108; I-44 to P-108; S-45 to P-108; S-46 to P-108; I-47 to P-108; G-48 to P-108; R-49 to P-108; G-50 to P-108; S-51 to P-108; E-52 to P-108; S-53 to P-108; V-54 to P-108; T-55 to P-108; S-56 to P-108; R-57 to P-108; G-58 to P-108; D-59 to P-108; L-60 to P-108; A-61 to P-108; T-62 to P-108; C-63 to P-108; P-64 to P-108; R-65 to P-108; G-66 to P-108; F-67 to P-108; A-68 to P-108; V-69 to P-108; T-70 to P-108; G-71 to P-108; C-72 to P-

108; T-73 to P-108; C-74 to P-108; G-75 to P-108; S-76 to P-108; A-77 to P-108; C-78 to P-108; G-79 to P-108; S-80 to P-108; W-81 to P-108; D-82 to P-108; V-83 to P-108; R-84 to P-108; A-85 to P-108; E-86 to P-108; T-87 to P-108; T-88 to P-108; C-89 to P-108; H-90 to P-108; C-91 to P-108; Q-92 to P-108; C-93 to P-108; A-94 to P-108; G-95 to P-108; M-96 to P-108; D-97 to P-108; W-98 to P-108; T-99 to P-108; G-100 to P-108; A-101 to P-108; R-102 to P-108; C-103 to P-108; of the GMAD sequence of SEQ ID NO:2.

[0079] As mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities such as the ability to induce resistance to cellular insulin and/or glucose uptake) may still be retained. For example the ability of the shortened GMAD polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the GMAD polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a GMAD polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six GMAD amino acid residues may often evoke an immune response.

[0080] In another embodiment, antibodies of the invention bind C-terminal deletions of the GMAD polypeptide that can be described by the general formula 1-m<sup>1</sup> where m<sup>1</sup> is a number from 7 to 102 corresponding to the amino acid sequence identified of SEQ ID NO:2. In specific embodiments, the invention provides antibodies that bind GMAD polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: M-1 to R-102; M-1 to A-101; M-1 to G-100; M-1 to T-99; M-1 to W-98; M-1 to D-97; M-1 to M-96; M-1 to G-95; M-1 to A-94; M-1 to C-93; M-1 to Q-92; M-1 to C-91; M-1 to H-90; M-1 to C-89; M-1 to T-88; M-1 to T-87; M-1 to E-86; M-1 to A-85; M-1 to R-84; M-1 to V-83; M-1 to D-82; M-1 to W-81; M-1 to S-80; M-1 to G-79; M-1 to C-78; M-1 to A-77; M-1 to S-76; M-1 to G-75; M-1 to C-74; M-1 to T-73; M-1 to C-72; M-1 to G-71; M-1 to T-70; M-1 to V-69; M-1 to A-68; M-1 to F-67; M-1 to G-66; M-1 to R-65; M-1 to P-64; M-1 to C-63; M-1 to T-62; M-1 to A-61; M-1 to L-60; M-1 to D-59; M-1 to G-58; M-1 to R-57; M-1 to S-56; M-1 to T-55; M-1 to V-54; M-1 to S-53; M-1 to E-52;

M-1 to S-51; M-1 to G-50; M-1 to R-49; M-1 to G-48; M-1 to I-47; M-1 to S-46; M-1 to S-45; M-1 to I-44; M-1 to A-43; M-1 to R-42; M-1 to F-41; M-1 to I-40; M-1 to L-39; M-1 to S-38; M-1 to G-37; M-1 to A-36; M-1 to V-35; M-1 to E-34; M-1 to Q-33; M-1 to I-32; M-1 to R-31; M-1 to E-30; M-1 to N-29; M-1 to I-28; M-1 to A-27; M-1 to E-26; M-1 to E-25; M-1 to M-24; M-1 to S-23; M-1 to C-22; M-1 to L-21; M-1 to T-20; M-1 to K-19; M-1 to S-18; M-1 to S-17; M-1 to V-16; M-1 to L-15; M-1 to L-14; M-1 to G-13; M-1 to L-12; M-1 to V-11; M-1 to P-10; M-1 to L-9; M-1 to L-8; M-1 to L-7; of the GMAD sequence of SEQ ID NO:2.

[0081] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a GMAD polypeptide, which may be described generally as having residues  $n^1$ - $m^1$  of SEQ ID NO:2, where  $n^1$ , and  $m^1$  are integers as described above.

[0082] Preferably, antibodies of the present invention bind fragments of GMAD comprising a portion of the secreted protein; i.e., within residues 21-108 of SEQ ID NO:2, since any portion therein is expected to be expressed, and secreted.

[0083] It will be recognized in the art that some amino acid sequence of GMAD can be varied without significant effect of the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the protein which determine activity. Such areas will usually comprise residues which make up the ligand binding site or which form tertiary structures which affect these domains.

[0084] Thus, the invention further includes antibodies that bind variations of the GMAD protein which show substantial GMAD protein activity or which include regions of GMAD such as the protein fragments discussed below. Such mutants include deletions, insertions, inversions, repeats, and type substitution. Guidance concerning which amino acid changes are likely to be phenotypically silent can be found in Bowie, J.U. *et al.*, *Science* 247:1306-1310 (1990).

[0085] Thus, antibodies of the present invention may bind a fragment, derivative, or analog of the polypeptide of SEQ ID NO:2, or that encoded by the GMAD cDNA in ATCC deposit 209215. Such fragments, variants or derivatives may be (i) one in which at least one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue(s), and more preferably at least one but less than ten conserved amino acid residues) and such

substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

[0086] Of particular interest are substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids. The latter results in proteins with reduced positive charge to improve the characteristics of the GMAD protein. The prevention of aggregation is highly desirable. Aggregation of proteins not only results in a loss of activity but can also be problematic when preparing pharmaceutical formulations, because they can be immunogenic. (Pinckard *et al.*, *Clin Exp. Immunol.* 2:331-340 (1967); Robbins *et al.*, *Diabetes* 36:838-845 (1987); Cleland *et al.* *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377 (1993)).

[0087] In addition, antibodies of the present invention may bind a GMAD polypeptide that contains one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation.

[0088] As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 3).

**TABLE 3. Conservative Amino Acid Substitutions.**

Aromatic	Phenylalanine Tryptophan Tyrosine
Hydrophobic	Leucine Isoleucine Valine
Polar	Glutamine Asparagine
Basic	Arginine Lysine Histidine
Acidic	Aspartic Acid Glutamic Acid
Small	Alanine Serine Threonine Methionine Glycine

[0089] In specific embodiments, the number of substitutions, additions or deletions in the amino acid sequence of SEQ ID NO:2 and/or any of the polypeptide fragments described herein is 75, 70, 60, 50, 40, 35, 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 30-20, 20-15, 20-10, 15-10, 10-1, 5-10, 1-5, 1-3 or 1-2.

[0090] In specific embodiments, the antibodies of the invention bind GMAD polypeptides or fragments or variants thereof (especially a fragment comprising or alternatively consisting of, the secreted, mature form of GMAD), that contains any one or more of the following conservative mutations in GMAD: M1 replaced with A, G, I, L, S, T, or V; K2 replaced with H, or R; A3 replaced with G, I, L, S, T, M, or V; L4 replaced with A, G, I, S, T, M, or V; L6 replaced with A, G, I, S, T, M, or V; L7 replaced with A, G, I, S, T, M, or V; L8 replaced with A, G, I, S, T, M, or V; L9 replaced with A, G, I, S, T, M, or V; V11 replaced with A, G, I, L, S, T, or M; L12 replaced with A, G, I, S, T, M, or V; G13 replaced with A, I, L, S, T, M, or V; L14 replaced with A, G, I, S, T, M, or V; L15 replaced with A, G, I, S, T, M, or V; V16 replaced with A, G, I, L, S, T, or M; S17 replaced with A, G, I, L, T, M, or V; S18 replaced with A, G, I, L, T, M, or V; K19

replaced with H, or R; T20 replaced with A, G, I, L, S, M, or V; L21 replaced with A, G, I, S, T, M, or V; S23 replaced with A, G, I, L, T, M, or V; M24 replaced with A, G, I, L, S, T, or V; E25 replaced with D; E26 replaced with D; A27 replaced with G, I, L, S, T, M, or V; I28 replaced with A, G, L, S, T, M, or V; N29 replaced with Q; E30 replaced with D; R31 replaced with H, or K; I32 replaced with A, G, L, S, T, M, or V; Q33 replaced with N; E34 replaced with D; V35 replaced with A, G, I, L, S, T, or M; A36 replaced with G, I, L, S, T, M, or V; G37 replaced with A, I, L, S, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; L39 replaced with A, G, I, S, T, M, or V; I40 replaced with A, G, L, S, T, M, or V; F41 replaced with W, or Y; R42 replaced with H, or K; A43 replaced with G, I, L, S, T, M, or V; I44 replaced with A, G, L, S, T, M, or V; S45 replaced with A, G, I, L, T, M, or V; S46 replaced with A, G, I, L, T, M, or V; I47 replaced with A, G, L, S, T, M, or V; G48 replaced with A, I, L, S, T, M, or V; R49 replaced with H, or K; G50 replaced with A, I, L, S, T, M, or V; S51 replaced with A, G, I, L, T, M, or V; E52 replaced with D; S53 replaced with A, G, I, L, T, M, or V; V54 replaced with A, G, I, L, S, T, or M; T55 replaced with A, G, I, L, S, M, or V; S56 replaced with A, G, I, L, T, M, or V; R57 replaced with H, or K; G58 replaced with A, I, L, S, T, M, or V; D59 replaced with E; L60 replaced with A, G, I, S, T, M, or V; A61 replaced with G, I, L, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; R65 replaced with H, or K; G66 replaced with A, I, L, S, T, M, or V; F67 replaced with W, or Y; A68 replaced with G, I, L, S, T, M, or V; V69 replaced with A, G, I, L, S, T, or M; T70 replaced with A, G, I, L, S, M, or V; G71 replaced with A, I, L, S, T, M, or V; T73 replaced with A, G, I, L, S, M, or V; G75 replaced with A, I, L, S, T, M, or V; S76 replaced with A, G, I, L, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; G79 replaced with A, I, L, S, T, M, or V; S80 replaced with A, G, I, L, T, M, or V; W81 replaced with F, or Y; D82 replaced with E; V83 replaced with A, G, I, L, S, T, or M; R84 replaced with H, or K; A85 replaced with G, I, L, S, T, M, or V; E86 replaced with D; T87 replaced with A, G, I, L, S, M, or V; T88 replaced with A, G, I, L, S, M, or V; H90 replaced with K, or R; Q92 replaced with N; A94 replaced with G, I, L, S, T, M, or V; G95 replaced with A, I, L, S, T, M, or V; M96 replaced with A, G, I, L, S, T, or V; D97 replaced with E; W98 replaced with F, or Y; T99 replaced with A, G, I, L, S, M, or V; G100 replaced with A, I, L, S, T, M, or V; A101 replaced with G, I, L, S, T, M, or V; R102 replaced with H, or K; R105 replaced with H, or K; V106 replaced with A, G, I, L, S, T, or M; and/or Q107 replaced with N; of SEQ ID NO:2.



[0091] In specific embodiments, the antibodies of the invention bind GMAD polypeptides or fragments or variants thereof (especially a fragment comprising or alternatively consisting of, the secreted, mature form of GMAD), that contains any one or more of the following non-conservative mutations in GMAD: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K2 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A3 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C5 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L6 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L7 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L8 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L9 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P10 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; V11 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L15 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S17 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S18 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T20 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L21 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C22 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S23 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E25 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A27 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N29 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E30 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R31 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I32 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q33 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E34 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V35 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G37 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I40 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F41 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R42 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F,

W, Y, P, or C; A43 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I44 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S46 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R49 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E52 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R57 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D59 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L60 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C63 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; P64 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R65 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G66 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F67 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A68 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G71 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C72 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; T73 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C74 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G75 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C78 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S80 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W81 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; D82 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V83 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R84 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A85 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E86 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T87 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T88 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C89 replaced with D, E, H, K, R, A,

G, I, L, S, T, M, V, N, Q, F, W, Y, or P; H90 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C91 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Q92 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; C93 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; A94 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G95 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M96 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D97 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W98 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T99 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G100 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R102 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C103 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C104 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; R105 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V106 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q107 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P108 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; of SEQ ID NO:2.

[0092] Amino acids in the GMAD protein of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as receptor binding or *in vitro*, or *in vivo* proliferative activity. Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol.* 224:899-904 (1992) and de Vos *et al.* *Science* 255:306-312 (1992)). In preferred embodiments, antibodies of the present invention bind regions of GMAD that are essential for GMAD function. In other preferred embodiments, antibodies of the present invention bind regions of GMAD that are essential for GMAD function and inhibit or abolish GMAD function. In other preferred embodiments, antibodies of the present invention bind regions of GMAD that are essential for GMAD function and enhance GMAD function.

[0093] Additionally, protein engineering may be employed to improve or alter the characteristics of GMAD polypeptides. Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or muteins including single or

multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. Antibodies of the present invention may bind such modified GMAD polypeptides.

[0094] Non-naturally occurring variants of GMAD may be produced using art-known mutagenesis techniques, which include, but are not limited to oligonucleotide mediated mutagenesis, alanine scanning, PCR mutagenesis, site directed mutagenesis (see e.g., Carter *et al.*, *Nucl. Acids Res.* 13:4331 (1986); and Zoller *et al.*, *Nucl. Acids Res.* 10:6487 (1982)), cassette mutagenesis (see e.g., Wells *et al.*, *Gene* 34:315 (1985)), restriction selection mutagenesis (see e.g., Wells *et al.*, *Philos. Trans. R. Soc. London SerA* 317:415 (1986)).

[0095] Thus, the invention also encompasses antibodies that bind GMAD derivatives and analogs that have one or more amino acid residues deleted, added, and/or substituted to generate GMAD polypeptides that are better suited for binding activity, therapeutic activity or expression, scale up, etc., in the host cells chosen. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges; N-linked glycosylation sites can be altered or eliminated to achieve, for example, expression of a homogeneous product that is more easily recovered and purified from yeast hosts which are known to hyperglycosylate N-linked sites. To this end, a variety of amino acid substitutions at one or both of the first or third amino acid positions on any one or more of the glycosylation recognition sequences in the GMAD polypeptides and/or an amino acid deletion at the second position of any one or more such recognition sequences will prevent glycosylation of GMAD at the modified tripeptide sequence (see, e.g., Miyajimo *et al.*, *EMBO J* 5(6):1193-1197). Additionally, one or more of the amino acid residues of GMAD polypeptides (e.g., arginine and lysine residues) may be deleted or substituted with another residue to eliminate undesired processing by proteases such as, for example, furins or kexins.

[0096] The antibodies of the present invention also include antibodies that bind a polypeptide comprising, or alternatively, consisting of, the polypeptide encoded by the deposited GMAD cDNA (the deposit having ATCC Accession Number 209215); a polypeptide comprising, or alternatively, consisting of, the polypeptide of SEQ ID NO:2 minus the amino terminal methionine; a polypeptide comprising, or alternatively,

consisting of the secreted form of GMAD; a polypeptide comprising, or alternatively, consisting of, the mature form of GMAD; as well as polypeptides which are at least 80% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptides described above (e.g., the polypeptide encoded by the deposited GMAD cDNA clone (the deposit having ATCC Accession Number 209215), the polypeptide of SEQ ID NO:2, and portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

[0097] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a GMAD polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of the GMAD polypeptide. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0098] As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in SEQ ID NO:2 or to the amino acid sequence encoded by deposited cDNA clones can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

[0099] In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global

sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case, the percent

identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

[0100] The present application is also directed to antibodies that bind proteins containing polypeptides at least 90%, 95%, 96%, 97%, 98% or 99% identical to the GMAD polypeptide sequence set forth herein as  $n^1-m^1$ . In preferred embodiments, the application is directed to antibodies that bind proteins containing polypeptides at least 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific GMAD N- and C-terminal deletions recited herein.

[0101] In certain preferred embodiments, antibodies of the invention bind GMAD fusion proteins as described above wherein the GMAD portion of the fusion protein are those described as  $n^1-m^1$  herein.

#### **Antibodies of the invention may bind Modified GMAD Polypeptides**

[0102] It is specifically contemplated that antibodies of the present invention may bind modified forms of the GMAD protein (SEQ ID NO:2)

[0103] In specific embodiments, antibodies of the present invention bind GMAD polypeptides (such as those described above) including, but not limited to naturally purified GMAD polypeptides, GMAD polypeptides produced by chemical synthetic procedures, and GMAD polypeptides produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells using, for example, the recombinant compositions and methods described above. Depending upon the host employed in a recombinant production procedure, the polypeptides may be glycosylated or non-glycosylated. In addition, GMAD polypeptides may also include an initial modified methionine residue, in some cases as a result of host-mediated processes.

[0104] In addition, GMAD proteins that antibodies of the present invention may bind can be chemically synthesized using techniques known in the art (e.g., see Creighton, *Proteins: Structures and Molecular Principles*, W.H. Freeman & Co., N.Y. (1983), and Hunkapiller, *et al.*, *Nature* 310:105-111 (1984)). For example, a peptide corresponding to a fragment of a GMAD polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino

acid analogs can be introduced as a substitution or addition into the GMAD polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0105] The invention additionally, encompasses antibodies that bind GMAD polypeptides which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited to, specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease,  $\text{NaBH}_4$ , acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin; etc.

[0106] Additional post-translational modifications to GMAD polypeptides for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[0107] Also provided by the invention are antibodies that bind chemically modified derivatives of GMAD polypeptide which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U. S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the



molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0108] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0109] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0110] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik *et al.*, *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues, glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene

glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0111] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a protein via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[0112] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (or peptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (*i.e.*, separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0113] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992); Francis *et al.*, *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[0114] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is

produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ( $\text{ClSO}_2\text{CH}_2\text{CF}_3$ ). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

[0115] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0116] The number of polyethylene glycol moieties attached to each GMAD polypeptide (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

[0117] As mentioned the antibodies of the present invention may bind GMAD polypeptides that are modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given GMAD polypeptide. GMAD polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic GMAD polypeptides may

result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter *et al.*, *Meth Enzymol* 182:626-646 (1990); Rattan *et al.*, *Ann NY Acad Sci* 663:48-62 (1992)).

#### **Anti-GMAD Antibodies:**

[0118] In one embodiment, the invention provides antibodies (e.g., antibodies comprising two heavy chains and two light chains linked together by disulfide bridges) that specifically bind a GMAD polypeptide (e.g., SEQ ID NO:2) or fragments or variants thereof, wherein the amino acid sequence of the heavy chain and the amino acid sequence of the light chain are the same as the amino acid sequence of a heavy chain and a light chain of one or more scFvs referred to in Table 1. In another embodiment, the invention provides antibodies (each consisting of two heavy chains and two light chains linked together by disulfide bridges to form an antibody) that specifically bind a GMAD polypeptide (e.g., SEQ ID NO:2) or fragments or variants thereof, wherein the amino acid sequence of the heavy chain or the amino acid sequence of the light chain are the same as the amino acid sequence of a heavy chain or a light chain of one or more scFvs referred to in Table 1. Specific binding to GMAD polypeptides may be determined by immunoassays known in the art or described herein for assaying specific antibody-antigen binding. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that specifically bind to GMAD are also encompassed by the invention, as are

nucleic acid molecules encoding these antibodies molecules, fragments and/or variants (e.g., SEQ ID NOS:137-233).

[0119] In one embodiment of the present invention, antibodies that specifically bind to GMAD or a fragment or variant thereof, comprise a polypeptide having the amino acid sequence of any one of the heavy chains of at least one of the scFvs referred to in Table 1 and/or any one of the light chains of at least one of the scFvs referred to in Table 1.

[0120] In another embodiment of the present invention, antibodies that specifically bind to GMAD or a fragment or variant thereof, comprise a polypeptide having the amino acid sequence of any one of the VH domains of at least one of the scFvs referred to in Table 1 and/or any one of the VL domains of at least one of the scFvs referred to in Table 1. In preferred embodiments, antibodies of the present invention comprise the amino acid sequence of a VH domain and VL domain from a single scFv referred to in Table 1. In alternative embodiments, antibodies of the present invention comprise the amino acid sequence of a VH domain and a VL domain from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, antibody fragments or variants of the VH and/or VL domains of at least one of the scFvs referred to in Table 1 that specifically bind to GMAD are also encompassed by the invention, as are nucleic acid molecules encoding these VH and VL domains, molecules, fragments and/or variants.

[0121] The present invention also provides antibodies that specifically bind to a polypeptide, or polypeptide fragment or variant of GMAD, wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the VH CDRs contained in a VH domain of one or more scFvs referred to in Table 1. In particular, the invention provides antibodies that specifically bind GMAD, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VH CDR1 contained in a VH domain of one or more scFvs referred to in Table 1. In another embodiment, antibodies that specifically bind GMAD, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR2 contained in a VH domain of one or more scFvs referred to in Table 1. In a preferred embodiment, antibodies that specifically bind GMAD, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR3 contained in a VH domain of one or more scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof, that

specifically bind to GMAD or a GMAD fragment or variant thereof are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants (e.g., SEQ ID NOS:137-233).

[0122] The present invention also provides antibodies that specifically bind to a polypeptide, or polypeptide fragment or variant of GMAD, wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the VL CDRs contained in a VL domain of one or more scFvs referred to in Table 1. In particular, the invention provides antibodies that specifically bind GMAD, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VL CDR1 contained in a VL domain of one or more scFvs referred to in Table 1. In another embodiment, antibodies that specifically bind GMAD, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR2 contained in a VL domain of one or more scFvs referred to in Table 1. In a preferred embodiment, antibodies that specifically bind GMAD, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR3 contained in a VL domain of one or more scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof, that specifically bind to GMAD or a GMAD fragment or variant are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants (e.g., SEQ ID NOS:137-233).

[0123] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that specifically bind to a GMAD polypeptide or polypeptide fragment or variant of GMAD, wherein said antibodies comprise, or alternatively consist of, one, two, three, or more VH CDRs and one, two, three or more VL CDRs, as contained in a VH domain or VL domain of one or more scFvs referred to in Table 1. In particular, the invention provides for antibodies that specifically bind to a polypeptide or polypeptide fragment or variant of GMAD, wherein said antibodies comprise, or alternatively consist of, a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VH CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any combination thereof, of the VH CDRs and VL CDRs contained in a VH domain or VL domain of one or more scFvs referred to in Table 1. In a preferred embodiment, one or more of these combinations are

from the same antibody as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that specifically bind to GMAD are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants (e.g., SEQ ID NOS:137-233).

#### **Nucleic Acid Molecules Encoding anti-GMAD Antibodies**

[0124] The present invention also provides for nucleic acid molecules, generally isolated, encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). In specific embodiments, the nucleic acid molecules encoding an antibody of the invention comprise, or alternatively consist of SEQ ID NOS:137-233 or fragments or variants thereof.

[0125] In a specific embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains of at least one of the scFvs referred to in Table 1 and a VL domain having an amino acid sequence of VL domain of at least one of the scFvs referred to in Table 1. In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains of at least one of the scFvs referred to in Table 1 or a VL domain having an amino acid sequence of a VL domain of at least one of the scFvs referred to in Table 1.

[0126] The present invention also provides antibodies that comprise, or alternatively consist of, variants (including derivatives) of the antibody molecules (e.g., the VH domains and/or VL domains) described herein, which antibodies specifically bind to GMAD or fragment or variant thereof. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid

substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity (*e.g.*, the ability to induce resistance to cellular insulin and/or glucose uptake).

[0127] For example, it is possible to introduce mutations only in framework regions or only in CDR regions of an antibody molecule. Introduced mutations may be silent or neutral missense mutations, *i.e.*, have no, or little, effect on an antibody's ability to bind antigen. These types of mutations may be useful to optimize codon usage, or improve a hybridoma's antibody production. Alternatively, non-neutral missense mutations may alter an antibody's ability to bind antigen. The location of most silent and neutral missense mutations is likely to be in the framework regions, while the location of most non-neutral missense mutations is likely to be in CDR, though this is not an absolute requirement. One of skill in the art would be able to design and test mutant molecules with desired properties such as no alteration in antigen binding activity or alteration in binding activity (*e.g.*, improvements in antigen binding activity or change in antibody specificity). Following mutagenesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein, (*e.g.*, ability to specifically bind GMAD) can be determined using techniques described herein or by routinely modifying techniques known in the art.

[0128] In a specific embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that specifically binds GMAD polypeptides or fragments or variants thereof,



comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH or VL domains of one or more scFvs referred to in Table 1, under stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6X sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C, or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds., 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0129] It is well known within the art that polypeptides, or fragments or variants thereof, with similar amino acid sequences often have similar structure and many of the same biological activities. Thus, in one embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that specifically binds to a GMAD polypeptide or a fragment or variant of a GMAD polypeptide, comprises, or alternatively consists of, a VH domain having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to the amino acid sequence of a VH domain of at least one of the scFvs referred to in Table 1.

[0130] In another embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that specifically binds to a GMAD polypeptide or a fragment or variant of a GMAD polypeptide, comprises, or alternatively consists of, a VL domain having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to the amino acid sequence of a VL domain of at least one of the scFvs referred to in Table 1.

## Methods of Producing Antibodies

[0131] Antibodies in accordance with the invention are preferably prepared using a phage scFv display library. Technologies utilized for achieving the same are disclosed in the patents, applications, and references disclosed herein.

[0132] In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (*e.g.*, human or murine cDNA libraries of lymphoid tissues) or synthetic cDNA libraries. The DNA encoding the VH and VL domains are joined together by an scFv linker by PCR and cloned into a phagemid vector (*e.g.*, p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to an antigen of interest (*i.e.*, a GMAD polypeptide or a fragment thereof) can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include, but are not limited to, those disclosed in Brinkman *et al.*, J. Immunol. Methods 182:41-50 (1995); Ames *et al.*, J. Immunol. Methods 184:177-186 (1995); Kettleborough *et al.*, Eur. J. Immunol. 24:952-958 (1994); Persic *et al.*, Gene 187 9-18 (1997); Burton *et al.*, Advances in Immunology 57:191-280(1994); PCT application No. PCT/GB91/O1 134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18719; WO 93/1 1236; WO 95/15982; WO 95/20401; WO97/13844; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,717; 5,780,225; 5,658,727; 5,735,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0133] For some uses, such as for in vitro affinity maturation of an antibody of the invention, it may be useful to express the VH and VL domains of one or more scFvs referred to in Table 1 as single chain antibodies or Fab fragments in a phage display library. For example, the cDNAs encoding the VH and VL domains of the scFvs referred to in Table 1 may be expressed in all possible combinations using a phage display library, allowing for the selection of VH/VL combinations that bind a GMAD polypeptide with preferred binding characteristics such as improved affinity or improved off rates.

Additionally, VH and VL segments - the CDR regions of the VH and VL domains of the scFvs referred to in Table 1, in particular, may be mutated in vitro. Expression of VH and VL domains with "mutant" CDRs in a phage display library allows for the selection of VH/VL combinations that bind a GMAD polypeptides with preferred binding characteristics such as improved affinity or improved off rates.

#### **Additional Methods of Producing Antibodies**

[0134] Antibodies of the invention (including antibody fragments or variants) can be produced by any method known in the art. For example, it will be appreciated that antibodies in accordance with the present invention can be expressed in cell lines including but not limited to myeloma cell lines and hybridoma cell lines. Sequences encoding the cDNAs or genomic clones for the particular antibodies can be used for transformation of a suitable mammalian or nonmammalian host cells or to generate phage display libraries, for example. Additionally, polypeptide antibodies of the invention may be chemically synthesized or produced through the use of recombinant expression systems.

[0135] One way to produce the antibodies of the invention would be to clone the VH and/or VL domains of the scFvs referred to in Table 1. In order to isolate the VH and VL domains from bacteria transfected with a vector containing the scFv, PCR primers complementary to VH or VL nucleotide sequences (See Example 2), may be used to amplify the VH and VL sequences. The PCR products may then be cloned using vectors, for example, which have a PCR product cloning site consisting of a 5' and 3' single T nucleotide overhang, that is complementary to the overhanging single adenine nucleotide added onto the 5' and 3' end of PCR products by many DNA polymerases used for PCR reactions. The VH and VL domains can then be sequenced using conventional methods known in the art. Alternatively, the VH and VL domains may be amplified using vector specific primers designed to amplify the entire scFv, (i.e. the VH domain, linker and VL domain.)

[0136] The cloned VH and VL genes may be placed into one or more suitable expression vectors. By way of non-limiting example, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site may be used to amplify the VH or VL sequences. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains may be cloned into vectors

expressing the appropriate immunoglobulin constant region, *e.g.*, the human IgG1 or IgG4 constant region for VH domains, and the human kappa or lambda constant regions for kappa and lambda VL domains, respectively. Preferably, the vectors for expressing the VH or VL domains comprise a promoter suitable to direct expression of the heavy and light chains in the chosen expression system, a secretion signal, a cloning site for the immunoglobulin variable domain, immunoglobulin constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into a single vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art (See, for example, Guo et al., *J. Clin. Endocrinol. Metab.* 82:925-31 (1997), and Ames et al., *J. Immunol. Methods* 184:177-86 (1995) which are herein incorporated in their entireties by reference).

[0137] The invention provides polynucleotides comprising, or alternatively consisting of, a nucleotide sequence encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). The invention also encompasses polynucleotides that hybridize under high stringency, or alternatively, under intermediate or lower stringency hybridization conditions, *e.g.*, as defined *supra*, to polynucleotides complementary to nucleic acids having a polynucleotide sequence that encodes an antibody of the invention or a fragment or variant thereof.

[0138] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. If the amino acid sequences of the VH domains, VL domains and CDRs thereof, are known, nucleotide sequences encoding these antibodies can be determined using methods well known in the art, *i.e.*, the nucleotide codons known to encode the particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody, of the invention. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier *et al.*, *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0139] Alternatively, a polynucleotide encoding an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (*e.g.*, an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells or Epstein Barr virus transformed B cell lines that express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0140] Once the nucleotide sequence of the antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, *e.g.*, recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook *et al.*, 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel *et al.*, eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0141] In a specific embodiment, VH and VL domains of heavy and light chains of one or more scFvs referred to in Table 1, or fragments or variants thereof, are inserted within framework regions using recombinant DNA techniques known in the art. In a specific embodiment, one, two, three, four, five, six, or more of the CDRs of heavy and light chains of one or more scFvs referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recombinant DNA techniques known in the art. The framework regions may be naturally occurring or consensus framework regions, and preferably are human framework regions (see, *e.g.*, Chothia *et al.*, J. Mol. Biol. 278: 457-

479 (1998) for a listing of human framework regions, the contents of which are hereby incorporated by reference in its entirety). Preferably, the polynucleotides generated by the combination of the framework regions and CDRs encode an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically binds to GMAD. Preferably, as discussed *supra*, polynucleotides encoding variants of antibodies or antibody fragments having one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions do not significantly alter binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules, or antibody fragments or variants, lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and fall within the ordinary skill of the art.

#### **XenoMouse Technology**

[0142] The ability to clone and reconstruct megabase-sized human loci in YACs and to introduce them into the mouse germline provides a powerful approach to elucidating the functional components of very large or crudely mapped loci as well as generating useful models of human disease. Furthermore, the utilization of such technology for substitution of mouse loci with their human equivalents could provide unique insights into the expression and regulation of human gene products during development, their communication with other systems, and their involvement in disease induction and progression.

[0143] An important practical application of such a strategy is the "humanization" of the mouse humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated offers the opportunity to study the mechanisms underlying programmed expression and assembly of antibodies as well as their role in B cell development. Furthermore, such a strategy could provide an ideal source for production of fully human monoclonal antibodies (Mabs) an important milestone towards fulfilling the promise of antibody therapy in human disease.

[0144] Fully human antibodies are expected to minimize the immunogenic and allergic responses intrinsic to mouse or mouse-derivatized Monoclonal antibodies and thus to increase the efficacy and safety of the administered antibodies. The use of fully human

antibodies can be expected to provide a substantial advantage in the treatment of chronic and recurring human diseases, such as cancer, which require repeated antibody administrations.

[0145] One approach towards this goal was to engineer mouse strains deficient in mouse antibody production with large fragments of the human Ig loci in anticipation that such mice would produce a large repertoire of human antibodies in the absence of mouse antibodies. Large human Ig fragments would preserve the large variable gene diversity as well as the proper regulation of antibody production and expression. By exploiting the mouse machinery for antibody diversification and selection and the lack of immunological tolerance to human proteins, the reproduced human antibody repertoire in these mouse strains should yield high affinity antibodies against any antigen of interest, including human antigens. Using the hybridoma technology, antigen-specific human Monoclonal antibodies with the desired specificity could be readily produced and selected.

[0146] This general strategy was demonstrated in connection with the generation of the first XenoMouse™ strains as published in 1994. *See Green et al. Nature Genetics* 7:13-21 (1994). The XenoMouse™ strains were engineered with yeast artificial chromosomes (YACS) containing 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus, respectively, which contained core variable and constant region sequences. *Id.* The human Ig containing YACs proved to be compatible with the mouse system for both rearrangement and expression of antibodies and were capable of substituting for the inactivated mouse Ig genes. This was demonstrated by their ability to induce B-cell development, to produce an adult-like human repertoire of fully human antibodies, and to generate antigen-specific human monoclonal antibodies. These results also suggested that introduction of larger portions of the human Ig loci containing greater numbers of V genes, additional regulatory elements, and human Ig constant regions might recapitulate substantially the full repertoire that is characteristic of the human humoral response to infection and immunization. The work of Green et al. was recently extended to the introduction of greater than approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and kappa light chain loci, respectively, to produce XenoMouse™ mice. *See Mendez et al. Nature Genetics* 15:146-156 (1997), Green and Jakobovits *J Exp. Med.* 188:483-495 (1998), Green, *Journal of Immunological Methods* 231:11-23 (1999) and U.S. Patent Application Serial

No. 08/759,620, filed December 3, 1996, the disclosures of which are hereby incorporated by reference.

[0147] Such approach is further discussed and delineated in U.S. Patent Application Serial Nos. 07/466,008, filed January 12, 1990, 07/710,515, filed November 8, 1990, 07/919,297, filed July 24, 1992, 07/922,649, filed July 30, 1992, filed 08/031,801, filed March 15, 1993, 08/112,848, filed August 27, 1993, 08/234,145, filed April 28, 1994, 08/376,279, filed January 20, 1995, 08/430, 938, April 27, 1995, 0-8/464,584, filed June 5, 1995, 08/464,582, filed June 5, 1995, 08/471,191, filed June 5, 1995, 08/462,837, filed June 5, 1995, 08/486,853, filed June 5, 1995, 08/486,857, filed June 5, 1995, 08/486,859, filed June 5, 1995, 08/462,513, filed June 5, 1995, 08/724,752, filed October 2, 1996, and 08/759,620, filed December 3, 1996. *See also* Mendez et al. *Nature Genetics* 15:146-156 (1997) and Green and Jakobovits *J Exp. Med.* 188:483-495 (1998). *See also* European Patent No., EP 0 471 151 B1, grant published June 12, 1996, International Patent Application No., WO 94/02602, published February 3, 1994, International Patent Application No., WO 96/34096, published October 31, 1996, and WO 98/24893, published June 11, 1998. The disclosures of each of the above-cited patents, applications, and references are hereby incorporated by reference in their entirety.

[0148] Human anti-mouse antibody (HAMA) responses have led the industry to prepare chimeric or otherwise humanized antibodies. While chimeric antibodies have a human constant region and a murine variable region, it is expected that certain human anti-chimeric antibody (HACA) responses will be observed, particularly in chronic or multi-dose utilizations of the antibody. Thus, it would be desirable to provide fully human antibodies against GMAD polypeptides in order to vitiate concerns and/or effects of HAMA or HACA responses.

[0149] Monoclonal antibodies specific for GMAD polypeptides may be prepared using hybridoma technology. (Kohler et al., *Nature* 256:495 (1975); Kohler et al., *Eur. J. Immunol.* 6:511 (1976); Kohler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, Elsevier, N.Y., pp. 571-681 (1981)). Briefly, mice such as XenoMouse™ mice may be immunized with GMAD polypeptides. After immunization, the splenocytes of such mice may be extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting



hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the GMAD polypeptides.

[0150] For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human patients. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50435, WO 98/24893, WO98/16654, WO 96/34096, WO 96/35735, and WO 91/10741; each of which is incorporated herein by reference in its entirety. In a specific embodiment, antibodies of the present invention comprise one or more VH and VL domains of the invention and constant regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In a specific embodiment, antibodies of the present invention comprise one or more CDRs corresponding to the VH and VL domains of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In other embodiments, an antibody of the present invention comprises one, two, three, four, five, six or more VL CDRs or VH CDRs corresponding to one or more of the VH or VL domains of one or more scFvs referred to in Table 1, or fragments or variants thereof, and framework regions (and, optionally one or more CDRs not present in the scFvs referred to in Table 1) from a human immunoglobulin molecule. In a preferred embodiment, an antibody of the present invention comprises a VH CDR3, VL CDR3, or both, corresponding to the same scFv, or different scFvs selected from the scFvs referred to in Table 1, or fragments or variants thereof, and framework regions from a human immunoglobulin.

[0151] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a human variable region and a non-human (e.g., murine) immunoglobulin constant region or vice versa. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi *et al.*, BioTechniques 4:214 (1986); Gillies *et al.*, J. Immunol. Methods 125:191-202 (1989); U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Chimeric antibodies comprising one or more CDRs from human species and framework regions from a non-human immunoglobulin molecule (e.g., framework regions from a murine,

canine or feline immunoglobulin molecule) (or vice versa) can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka *et al.*, *Protein Engineering* 7(6):805-814 (1994); Roguska *et al.*, *PNAS* 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,352). In a preferred embodiment, chimeric antibodies comprise a human CDR3 having an amino acid sequence of any one of the VH CDR3s or VL CDR3s of a VH or VL domain of one or more of the scFvs referred to in Table 1, or a variant thereof, and non-human framework regions or human framework regions different from those of the frameworks in the corresponding scFvs disclosed in Table 1. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, *e.g.*, Queen *et al.*, U.S. Patent No. 5,585,089; Riechmann *et al.*, *Nature* 352:323 (1988), which are incorporated herein by reference in their entireties.)

[0152] Intrabodies are antibodies, often scFvs, that are expressed from a recombinant nucleic acid molecule and engineered to be retained intracellularly (*e.g.*, retained in the cytoplasm, endoplasmic reticulum, or periplasm). Intrabodies may be used, for example, to ablate the function of a protein to which the intrabody binds. The expression of intrabodies may also be regulated through the use of inducible promoters in the nucleic acid expression vector comprising the intrabody. Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen *et al.*, *Hum. Gene Ther.* 5:595-601 (1994); Marasco, W.A., *Gene Ther.* 4:11-15 (1997); Rondon and Marasco, *Annu. Rev. Microbiol.* 51:257-283 (1997); Proba *et al.*, *J. Mol. Biol.* 275:245-253 (1998); Cohen *et al.*, *Oncogene* 17:2445-2456 (1998); Ohage and Steipe, *J. Mol. Biol.* 291:1119-1128 (1999); Ohage *et al.*, *J. Mol. Biol.* 291:1129-1134 (1999); Wirtz and Steipe, *Protein Sci.* 8:2245-2250 (1999); Zhu *et al.*, *J. Immunol. Methods* 231:207-222 (1999); and references cited therein.

[0153] Recombinant expression of an antibody of the invention (including antibody fragments or variants thereof (*e.g.*, a heavy or light chain of an antibody of the

invention), requires construction of an expression vector(s) containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule (e.g., a whole antibody, a heavy or light chain of an antibody, or portion thereof (preferably, but not necessarily, containing the heavy or light chain variable domain)), of the invention has been obtained, the vector(s) for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention (e.g., a whole antibody, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody, or a portion thereof, or a heavy or light chain CDR, a single chain Fv, or fragments or variants thereof), operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464, the contents of each of which are hereby incorporated by reference in its entirety) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy chain, the entire light chain, or both the entire heavy and light chains.

[0154] The expression vector(s) is(are) transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing polynucleotide(s) encoding an antibody of the invention (e.g., whole antibody, a heavy or light chain thereof, or portion thereof, or a single chain antibody, or a fragment or variant thereof), operably linked to a heterologous promoter. In preferred embodiments, for the expression of entire antibody molecules, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0155] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by

which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention *in situ*. These include, but are not limited to, bacteriophage particles engineered to express antibody fragments or variants thereof (single chain antibodies), microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3, NS0 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking *et al.*, Gene 45:101 (1986); Cockett *et al.*, Bio/Technology 8:2 (1990); Bebbington *et al.*, Bio/Techniques 10:169 (1992); Keen and Hale, Cytotechnology 18:207 (1996)). These references are incorporated in their entireties by reference herein.

[0156] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther *et al.*, EMBO 1. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a

fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione 5-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0157] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) may be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. Antibody coding sequences may be cloned individually into non-essential regions (for example, the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example, the polyhedrin promoter).

[0158] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (*e.g.*, see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, *e.g.*, Bittner *et al.*, Methods in Enzymol. 153:51-544 (1987)).

[0159] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different

host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERY, BHK, HeLa, COS, NSO, MDCK, 293, 3T3, and W138.

[0160] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

[0161] A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler *et al.*, Cell 11:223 (1977)), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy *et al.*, Cell 22:8 17 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler *et al.*, Natl. Acad. Sci. USA 77:357 (1980); O'Hare *et al.*, Proc. Natl. Acad. Sci. USA 78:1527 (1981)); *gpt*, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); *neo*, which confers resistance to the aminoglycoside G-418 (Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and

Anderson, *Ann. Rev. Biochem.* 62: 191-217 (1993); TIB TECH 11(5):155-2 15 (May, 1993)); and *hygro*, which confers resistance to hygromycin (Santerre *et al.*, *Gene* 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel *et al.* (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli *et al.* (eds), *Current Protocols in Human Genetics*, John Wiley & Sons, NY (1994); Colberre-Garapin *et al.*, *J. Mol. Biol.* 150:1 (1981), which are incorporated by reference herein in their entireties.

[0162] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, "The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells" in *DNA Cloning, Vol.3.* (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the coding sequence of the antibody, production of the antibody will also increase (Crouse *et al.*, *Mol. Cell. Biol.* 3:257 (1983)).

[0163] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entireties by reference herein.

[0164] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain is preferably placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2 197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0165] Once an antibody molecule of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) has been chemically synthesized or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, a protein molecule, such as, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[0166] Antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the antibodies of the present invention may be glycosylated or may be non-glycosylated. In addition, antibodies of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes.

[0167] Antibodies of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller, M., et al., 1984, Nature 310:105-111). For example, a peptide corresponding to a fragment of an antibody of the invention can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into



the antibody polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid,  $\gamma$ -Abu,  $\epsilon$ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine,  $\beta$ -alanine, fluoro-amino acids, designer amino acids such as  $\beta$ -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0168] The invention encompasses antibodies which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease,  $\text{NaBH}_4$ , acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin, etc.

[0169] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The antibodies may also be modified with a detectable label, such as an enzymatic, fluorescent, radioisotopic or affinity label to allow for detection and isolation of the antibody.

[0170] Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, glucose oxidase or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include biotin, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include a radioactive metal ion, e.g., alpha-emitters such as,

for example,  $^{213}\text{Bi}$ , or other radioisotopes such as, for example, iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{75}\text{Se}$ ,  $^{113}\text{Sn}$ , and  $^{117}\text{Tm}$ .

[0171] In specific embodiments, antibodies of the invention may be labeled with Europium. For example, antibodies of the invention may be labelled with Europium using the DELFIA Eu-labeling kit (catalog# 1244-302, Perkin Elmer Life Sciences, Boston, MA) following manufacturer's instructions.

[0172] In specific embodiments, antibodies of the invention are attached to macrocyclic chelators useful for conjugating radiometal ions, including but not limited to,  $^{111}\text{In}$ ,  $^{177}\text{Lu}$ ,  $^{90}\text{Y}$ ,  $^{166}\text{Ho}$ ,  $^{153}\text{Sm}$ ,  $^{215}\text{Bi}$  and  $^{225}\text{Ac}$  to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is  $^{111}\text{In}$ . In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator attached to antibodies polypeptides of the invention is  $^{90}\text{Y}$ . In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In specific embodiments, the macrocyclic chelator is  $\alpha$ -(5-isothiocyanato-2-methoxyphenyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid. In other specific embodiments, the DOTA is attached to the antibody of the invention via a linker molecule. Examples of linker molecules useful for conjugating a macrocyclic chelator such as DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90, 1998; Peterson et al., Bioconjug. Chem. 10(4):553-7, 1999; and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety. In addition, U.S. Patents 5,652,361 and 5,756,065, which disclose chelating agents that may be conjugated to antibodies, and methods for making and using them, are hereby incorporated by reference in their entireties.

[0173] In one embodiment, antibodies of the invention are labeled with biotin. In other related embodiments, biotinylated antibodies of the invention may be used, for example, as an imaging agent or as a means of identifying one or more TRAIL receptor coreceptor or ligand molecules.

[0174] Also provided by the invention are chemically modified derivatives of antibodies of the invention which may provide additional advantages such as increased solubility, stability and in vivo or in vitro circulating time of the polypeptide, or decreased immunogenicity (see U. S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The antibodies may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0175] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0176] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti et al., *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0177] The polyethylene glycol molecules (or other chemical moieties) should be attached to the antibody with consideration of effects on functional or antigenic domains of the antibody. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF

using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include, for example, lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues, glutamic acid residues, and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0178] As suggested above, polyethylene glycol may be attached to proteins, e.g., antibodies, via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[0179] One may specifically desire antibodies chemically modified at the N-terminus of either the heavy chain or the light chain or both. Using polyethylene glycol as an illustration, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (or peptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective chemical modification at the N-terminus may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0180] As indicated above, pegylation of the antibodies of the invention may be accomplished by any number of means. For example, polyethylene glycol may be

attached to the antibody either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992); Francis et al., *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[0181] One system for attaching polyethylene glycol directly to amino acid residues of antibodies without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ( $\text{ClSO}_2\text{CH}_2\text{CF}_3$ ). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes antibody-polyethylene glycol conjugates produced by reacting antibodies of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

[0182] Polyethylene glycol can also be attached to antibodies using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Antibody-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the antibody by a linker can also be produced by reaction of antibodies with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated antibody products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0183] The number of polyethylene glycol moieties attached to each antibody of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated antibodies of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per

antibody molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

### Characterization of anti-GMAD Antibodies

[0184] Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be described or specified in terms of their binding to GMAD polypeptides or fragments or variants of GMAD polypeptides. In specific embodiments, antibodies of the invention bind GMAD polypeptides, or fragments or variants thereof, with a dissociation constant or  $K_D$  of less than or equal to  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M, or  $10^{-5}$  M. More preferably, antibodies of the invention bind GMAD polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M, or  $10^{-8}$  M. Even more preferably, antibodies of the invention bind GMAD polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M. The invention encompasses antibodies that bind GMAD polypeptides with a dissociation constant or  $K_D$  that is within any one of the ranges that are between each of the individual recited values.

[0185] In specific embodiments, antibodies of the invention bind GMAD polypeptides or fragments or variants thereof with an off rate ( $k_{off}$ ) of less than or equal to  $5 \times 10^{-2}$  sec $^{-1}$ ,  $10^{-2}$  sec $^{-1}$ ,  $5 \times 10^{-3}$  sec $^{-1}$  or  $10^{-3}$  sec $^{-1}$ . More preferably, antibodies of the invention bind GMAD polypeptides or fragments or variants thereof with an off rate ( $k_{off}$ ) less than or equal to  $5 \times 10^{-4}$  sec $^{-1}$ ,  $10^{-4}$  sec $^{-1}$ ,  $5 \times 10^{-5}$  sec $^{-1}$ , or  $10^{-5}$  sec $^{-1}$ .  $5 \times 10^{-6}$  sec $^{-1}$ ,  $10^{-6}$  sec $^{-1}$ ,  $5 \times 10^{-7}$  sec $^{-1}$  or  $10^{-7}$  sec $^{-1}$ . The invention encompasses antibodies that bind GMAD polypeptides with an off rate ( $k_{off}$ ) that is within any one of the ranges that are between each of the individual recited values.

[0186] In other embodiments, antibodies of the invention bind GMAD polypeptides or fragments or variants thereof with an on rate ( $k_{on}$ ) of greater than or equal to  $10^3$  M $^{-1}$  sec $^{-1}$ ,  $5 \times 10^3$  M $^{-1}$  sec $^{-1}$ ,  $10^4$  M $^{-1}$  sec $^{-1}$  or  $5 \times 10^4$  M $^{-1}$  sec $^{-1}$ . More preferably, antibodies of the invention bind GMAD polypeptides or fragments or variants thereof with an on rate ( $k_{on}$ ) greater than or equal to  $10^5$  M $^{-1}$  sec $^{-1}$ ,  $5 \times 10^5$  M $^{-1}$  sec $^{-1}$ ,  $10^6$  M $^{-1}$  sec $^{-1}$ , or  $5 \times 10^6$  M $^{-1}$  sec $^{-1}$  or  $10^7$  M $^{-1}$  sec $^{-1}$ . The invention encompasses antibodies that bind GMAD

polypeptides with on rate ( $k_{on}$ ) that is within any one of the ranges that are between each of the individual recited values.

[0187] The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) specifically bind to a polypeptide or polypeptide fragment or variant of a human GMAD polypeptide (SEQ ID NO:2). In another embodiment, the antibodies of the invention specifically bind to a polypeptide or polypeptide fragment or variant of a simian GMAD polypeptide. In yet another embodiment, the antibodies of the invention specifically bind to a polypeptide or polypeptide fragment or variant of a murine GMAD polypeptide. In one embodiment, the antibodies of the invention bind specifically to human and simian GMAD polypeptides. In another embodiment, the antibodies of the invention bind specifically to human GMAD polypeptides and murine GMAD polypeptides. More preferably, antibodies of the invention, preferentially bind to human GMAD polypeptides compared to murine GMAD polypeptides.

[0188] In preferred embodiments, the antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), specifically bind to GMAD polypeptides and do not cross-react with any other antigens. In preferred embodiments, the antibodies of the invention specifically bind to GMAD polypeptides (e.g., SEQ ID NO:2 or fragments or variants thereof) and do not cross-react with one or more GMAD-related (e.g., other FIZZ or RELM family) polypeptides.

[0189] By way of non-limiting example, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with a dissociation constant ( $K_D$ ) that is less than the antibody's  $K_D$  for the second antigen. In another non-limiting embodiment, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with an affinity (i.e.,  $K_D$ ) that is at least one order of magnitude less than the antibody's  $K_D$  for the second antigen. In another non-limiting embodiment, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with an affinity (i.e.,  $K_D$ ) that is at least two orders of magnitude less than the antibody's  $K_D$  for the second antigen.

[0190] In another non-limiting embodiment, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with an off rate ( $k_{off}$ ) that is less than the antibody's  $k_{off}$  for the second antigen. In another non-limiting embodiment,

an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with a  $k_{off}$  that is at least one order of magnitude less than the antibody's  $k_{off}$  for the second antigen. In another non-limiting embodiment, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with a  $k_{off}$  that is at least two orders of magnitude less than the antibody's  $k_{off}$  for the second antigen.

[0191] The invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that have one or more of the same biological characteristics as one or more of the antibodies described herein. By "biological characteristics" is meant, the in vitro or in vivo activities or properties of the antibodies, such as, for example, the ability to antagonize GMAD action (see, e.g., Example 3), the ability to increase insulin action, the ability to increase cellular uptake of insulin, the ability increase cellular uptake of glucose (e.g. glucose transport), the ability to inhibit cell-specific (e.g., adipocytes) GMAD secretion, and/or the ability to inhibit differentiation of GMAD or GMAD receptor expressing cells (e.g., adipocytes). Other biological activities that anti-GMAD antibodies may have, include, but are not limited to, the ability to stimulate GMAD mediated biological activity (e.g., the ability to decrease insulin action.) Optionally, the antibodies of the invention will bind to the same epitope as at least one of the antibodies specifically referred to herein. Such epitope binding can be routinely determined using assays known in the art.

[0192] The present invention provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit one or more GMAD polypeptide mediated biological activities. In one embodiment, an antibody that inhibits one or more GMAD polypeptide mediated biological activities comprises, or alternatively consists of, a VH and/or a VL domain of at least one of the scFvs referred to in Table 1, or fragment or variant thereof. In a specific embodiment, an antibody that inhibits one or more GMAD polypeptide mediated biological activities comprises, or alternatively consists of, a VH and a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0193] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that increase insulin action. In one embodiment, an antibody that increases insulin action comprises, or alternatively consists of, a VH and/or a VL domain of any one of the scFvs



referred to in Table 1, or fragment or variant thereof. In a specific embodiment, an antibody that increases insulin action comprises, or alternatively consists of, a VH and a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0194] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that increase cellular glucose uptake. In one embodiment, an antibody that increases cellular glucose uptake comprises, or alternatively consists of, a VH and/or a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. In a specific embodiment, an antibody that increases cellular glucose uptake comprises, or alternatively consists of, a VH and a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0195] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that decrease cell-specific (e.g., adipocytes) GMAD expression. In one embodiment, an antibody that decreases cell-specific (e.g., adipocyte) GMAD expression, or alternatively consists of, a VH and/or a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. In a specific embodiment, an antibody that decreases cell-specific (e.g., adipocyte) GMAD expression comprises, or alternatively consists of, a VH and a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0196] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit differentiation of GMAD or GMAD receptor expressing cells (e.g., adipocyte). In one embodiment, an antibody that inhibits differentiation of GMAD or GMAD receptor expressing cells comprises, or alternatively consists of, a VH and/or a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. In a specific embodiment, an antibody that inhibits differentiation of GMAD or GMAD receptor expressing cells comprises, or alternatively consists of, a VH and a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0197] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), which decrease insulin action. In one embodiment, an antibody that decreases insulin action comprises, or alternatively consists of, a VH and/or a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. In a specific embodiment, an antibody that decreases insulin action comprises, or alternatively consists of, a VH and a VL domain of any one of the scFvs referred to in Table 1, or fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0198] Antibodies of the present invention (including antibody fragments or variants thereof) may be characterized in a variety of ways. In particular, antibodies and related molecules of the invention may be assayed for the ability to specifically bind to GMAD polypeptides or a fragment or variant of a GMAD polypeptide using techniques described herein or routinely modifying techniques known in the art. Assays for the ability of the antibodies of the invention to specifically bind GMAD polypeptides or a fragment of GMAD polypeptides may be performed in solution (*e.g.*, Houghten, *Bio/Techniques* 13:412-421(1992)), on beads (*e.g.*, Lam, *Nature* 354:82-84 (1991)), on chips (*e.g.*, Fodor, *Nature* 364:555-556 (1993)), on bacteria (*e.g.*, U.S. Patent No. 5,223,409), on spores (*e.g.*, Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (*e.g.*, Cull et al., *Proc. Natl. Acad. Sci. USA* 89:1865-1869 (1992)) or on phage (*e.g.*, Scott and Smith, *Science* 249:386-390 (1990); Devlin, *Science* 249:404-406 (1990); Cwirla et al., *Proc. Natl. Acad. Sci. USA* 87:7178-7182 (1990); and Felici, *J. Mol. Biol.* 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). Such assays may be used to identify antibodies that specifically bind to GMAD polypeptides or a fragment or variant of a GMAD polypeptide.

[0199] The antibodies of the invention may be assayed for specific binding to GMAD polypeptides and cross-reactivity with other antigens by any method known in the art. Immunoassays which can be used to analyze specific binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as BIAcore analysis, FACS (fluorescence activated cell sorter) analysis, immunofluorescence, immunocytochemistry, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, western blots, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent

immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al., eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0200] ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound antibodies or non-specifically bound antibodies, and detecting the presence of the antibodies specifically bound to the antigen coating the well. In ELISAs, the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Alternatively, the antigen need not be directly coated to the well; instead the ELISA plates may be coated with an anti-Ig Fc antibody, and the antigen, in the form of a GMAD-Fc fusion protein, may be bound to the anti-Ig Fc coated to the plate. This may be desirable so as to maintain the antigen protein (*e.g.*, a GMAD polypeptide) in a more native conformation than it may have when it is directly coated to a plate. In another alternative, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al., eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

[0201] The binding affinity of an antibody (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*, antigen labeled with  $^3\text{H}$  or  $^{125}\text{I}$ ), or fragment or variant thereof with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the

labeled antigen. The affinity of the antibody of the present invention for GMAD and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, GMAD polypeptide is incubated with an antibody of the present invention conjugated to a labeled compound (e.g., compound labeled with  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second anti-GMAD antibody. This kind of competitive assay between two antibodies, may also be used to determine if two antibodies bind the same, closely associated (e.g, overlapping), or different epitopes.

[0202] In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibodies (including antibody fragments or variants thereof) to GMAD, or fragments of GMAD. BIAcore kinetic analysis comprises analyzing the binding and dissociation of antibodies from chips with immobilized GMAD on their surface.

[0203] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1 to 4 hours) at 40 degrees C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

[0204] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the

membrane in washing buffer (*e.g.*, PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, *e.g.*, an anti-human antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al., eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

### Antibody Conjugates

[0205] The present invention encompasses antibodies (including antibody fragments or variants thereof), recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous polypeptide (or portion thereof, preferably at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids of the polypeptide) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies of the invention may be used to target heterologous polypeptides to particular cell types (*e.g.*, cancer cells), either *in vitro* or *in vivo*, by fusing or conjugating the heterologous polypeptides to antibodies of the invention that are specific for particular cell surface antigens or which bind antigens that bind particular cell surface receptors. Antibodies of the invention may also be fused to albumin (including but not limited to recombinant human serum albumin (see, *e.g.*, U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (*i.e.*, amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments

comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention. Such fusion proteins may, for example, facilitate purification and may increase half-life *in vivo*. Antibodies fused or conjugated to heterologous polypeptides may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See *e.g.*, Harbor *et al.*, *supra*, and PCT publication WO 93/2 1232; EP 439,095; Naramura *et al.*, Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies *et al.*, PNAS 89:1428-1432 (1992); Fell *et al.*, J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

[0206] The present invention further includes compositions comprising, or alternatively consisting of, heterologous polypeptides fused or conjugated to antibody fragments. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, F(ab)<sub>2</sub> fragment, or a portion thereof. Methods for fusing or conjugating polypeptides to antibody portions are known in the art. See, *e.g.*, U.S. Patent Nos. 5,356,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 9 1/06570; Ashkenazi *et al.*, Proc. Natl. Acad. Sci. USA 88: 10535-10539 (1991); Zheng *et al.*, J. Immunol. 154:5590-5600 (1995); and Vil *et al.*, Proc. Natl. Acad. Sci. USA 89:11357- 11341 (1992) (said references incorporated by reference in their entireties).

[0207] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), such methods can be used to generate antibodies with altered activity (*e.g.*, antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten *et al.*, Curr. Opinion Biotechnol. 8:724-35 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, *et al.*, J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998) (each of these

patents and publications are hereby incorporated by reference in its entirety). In one embodiment, polynucleotides encoding antibodies of the invention may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more portions of a polynucleotide encoding an antibody which portions specifically bind to GMAD may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[0208] Moreover, the antibodies of the present invention (including antibody fragments or variants thereof) can be fused to marker sequences, such as a polypeptides to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine polypeptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, Cell 37:767 (1984)) and the FLAG® tag (Stratagene, La Jolla, CA).

[0209] The present invention further encompasses antibodies (including antibody fragments or variants thereof), conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor or prognose the development or progression of a tumor as part of a clinical testing procedure or monitor or prognose type II diabetes to, *e.g.*, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include, but are not limited to, various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include, but are not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes

include, but are not limited to, streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include, but are not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes, but is not limited to, luminol; examples of bioluminescent materials include, but are not limited to, luciferase, luciferin, and aequorin; and examples of suitable radioactive material include, but are not limited to, iodine ( $^{121}\text{I}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{111}\text{In}$ ,  $^{112}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{115\text{m}}\text{In}$ ), technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{135}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ , and  $^{97}\text{Ru}$ .

[0210] Further, an antibody of the invention (including antibody fragments or variants thereof), may be coupled or conjugated to a therapeutic moiety such as a cytotoxin, *e.g.*, a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, *e.g.*, alpha-emitters such as, for example,  $^{213}\text{Bi}$ , or other radioisotopes such as, for example,  $^{103}\text{Pd}$ ,  $^{135}\text{Xe}$ ,  $^{131}\text{I}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{90}\text{Y}$ ,  $^{153}\text{Sm}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{75}\text{Se}$ ,  $^{113}\text{Sn}$ ,  $^{90}\text{Y}$ ,  $^{117}\text{Tm}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$  and  $^{166}\text{Ho}$ . In specific embodiments, an antibody or fragment thereof is attached to macrocyclic chelators that chelate radiometal ions, including but not limited to,  $^{177}\text{Lu}$ ,  $^{90}\text{Y}$ ,  $^{166}\text{Ho}$ , and  $^{153}\text{Sm}$ , to polypeptides. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane- $\text{N,N',N'',N'''}\text{-tetraacetic acid (DOTA)}$ . In other specific embodiments, the DOTA is attached to the antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., *Clin Cancer Res.* 4(10):2483-90, 1998; Peterson et al., *Bioconjug. Chem.* 10(4):553-7, 1999; and Zimmerman et al., *Nucl. Med. Biol.* 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety.

[0211] A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include, but are not limited to, paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, thymidine kinase, endonuclease, RNase, and puromycin and fragments, variants or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-



fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

[0212] Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see *e.g.*, U.S. Patent Nos. 5,756,065; 5,714,711; 5,696,239; 5,652,371; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety) and direct coupling reactions (*e.g.*, Bolton-Hunter and Chloramine-T reaction).

[0213] The antibodies of the invention which are conjugates can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, but are not limited to, for example, a toxin such as abrin, ricin A, alpha toxin, pseudomonas exotoxin, or diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, *e.g.*, TNF-alpha, TNF-beta, AIM I (see, International Publication No. WO 97/35899), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, *e.g.*, angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), or other growth factors.

[0214] Antibodies of the invention (including antibody fragments or variants thereof), may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0215] Techniques for conjugating a therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

[0216] Alternatively, an antibody of the invention can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0217] An antibody of the invention (including an other molecules comprising, or alternatively consisting of, an antibody fragment or variant thereof), with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

#### **Uses of Antibodies of the Invention**

[0218] Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of GMAD polypeptides in biological samples. See, e.g., Harlow *et al.*, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

#### **Immunophenotyping**

[0219] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker

that is differentially expressed at various stages of differentiation and/or maturation of particular cell types, particularly of adipose cells. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

[0220] These techniques allow for the screening of particular populations of cells, such as adipocytes (e.g., in Type I or II diabetes patients). Alternatively, these techniques allow for the screening of mast cells, eosinophils, lymphocytes and bronchial tissue for the expression of GMAD.

#### **Epitope Mapping**

[0221] The present invention provides antibodies (including antibody fragments or variants thereof), which can be used to identify epitopes of a GMAD polypeptide. In particular, the antibodies of the present invention can be used to identify epitopes of a human GMAD polypeptide (e.g., SEQ ID NO:2) or a GMAD polypeptide expressed on human cells; a murine GMAD or a GMAD polypeptide expressed on murine cells; a rat GMAD polypeptide or a GMAD polypeptide expressed on rat cells; or a monkey GMAD polypeptide or a GMAD polypeptide expressed on monkey cells, using techniques described herein or otherwise known in the art. Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,711,211.) Identified epitopes of antibodies of the present invention may, for example, be used as vaccine candidates, i.e., to immunize an individual to elicit antibodies against the naturally occurring forms of GMAD polypeptides.

#### **Diagnostic Uses of Antibodies**

[0222] Labeled antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to a GMAD polypeptide can be used for diagnostic purposes to detect, diagnose, prognose, or monitor diseases and/or disorders. In specific embodiments, labeled antibodies of the

invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to a GMAD polypeptide can be used for diagnostic purposes to detect, diagnose, prognose, or monitor diseases and/or disorders associated with the aberrant expression and/or activity of a GMAD polypeptide.

[0223] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. In certain embodiments, the disorder diagnosed according to a method of the invention is selected from the group: diabetes (e.g., Non-Insulin-Dependent Diabetes Mellitus (NIDDM)), insulin insensitivity (i.e., insulin resistance), hyperinsulinemia, hyperglycemia, dyslipidemia, hypertension, coronary artery disease, renal failure, neuropathy (e.g., autonomic neuropathy, parasympathetic neuropathy, and polyneuropathy), a metabolic disorder (e.g., a glucose metabolic disorder), an endocrine disorder, obesity, weight loss, a liver disorder (e.g., liver disease, cirrhosis of the liver, and a disorder associated with liver transplant), and/or a condition associated with one or more of these disorders.

[0224] In particular embodiments, the invention provides a diagnostic method of a metabolic disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a metabolic disorder.

[0225] In other embodiments, the invention provides a diagnostic method useful for diagnosis of insulin responsiveness, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase in the assayed polypeptide expression level compared to the standard expression level is indicative of an insulin responsiveness disorder (e.g., insulin resistance).

[0226] In other embodiments, the invention provides a diagnostic method useful for diagnosis of diabetes, which involves (a) assaying the expression level of a polypeptide

of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase in the assayed polypeptide expression level compared to the standard expression level is indicative of diabetes.

[0227] In other embodiments, the invention provides a diagnostic method useful for diagnosis and/or prognosis of a predisposition for diabetes, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby a decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a predisposition for diabetes.

[0228] The invention provides for the detection of expression of a GMAD polypeptide comprising: (a) assaying the expression of a GMAD polypeptide in a biological sample from an individual using one or more antibodies of the invention that specifically binds to a GMAD polypeptide; and (b) comparing the level of a GMAD polypeptide with a standard level of a GMAD polypeptide, (*e.g.*, the level in normal biological samples).

[0229] The invention provides for the detection of aberrant expression of a GMAD polypeptide comprising: (a) assaying the expression of a GMAD polypeptide in a biological sample from an individual using one or more antibodies of the invention that specifically binds to a GMAD polypeptide; and (b) comparing the level of a GMAD polypeptide with a standard level of a GMAD polypeptide, *e.g.*, in normal biological samples, whereby an increase or decrease in the assayed level of a GMAD polypeptide compared to the standard level of a GMAD polypeptide is indicative of aberrant expression.

[0230] By "biological sample" is intended any fluids and/or cells obtained from an individual, body fluid, body tissue, body cell, cell line, tissue culture, or other source that may contain a GMAD polypeptide protein or mRNA. Body fluids include, but are not limited to, sera, plasma, urine, synovial fluid, spinal fluid, saliva, and mucous. Tissues samples may be taken from virtually any tissue in the body. Tissue samples may also be obtained from autopsy material. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0231] One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a GMAD polypeptide or a GMAD polypeptide receptor in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically binds to a GMAD polypeptide; b) waiting for a time interval following the administering for permitting the labeled antibody to preferentially concentrate at sites in the subject where GMAD polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled antibody in the subject, such that detection of labeled antibody or fragment thereof above the background level and above or below the level observed in a person without the disease or disorder indicates that the subject has a particular disease or disorder associated with aberrant expression of a GMAD polypeptide or a GMAD polypeptide receptor. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0232] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99</sup>Tc. The labeled antibody will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel *et al.*, "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

[0233] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0234] In one embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0235] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0236] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston *et al.*, U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

#### **Therapeutic Uses of Antibodies**

[0237] One or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to GMAD may be used locally or systemically in the body as a therapeutic. The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) to an animal, preferably a mammal, and most preferably a human, for preventing or treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention and nucleic acids encoding antibodies (and anti-idiotypic antibodies) of the invention as described herein. In one embodiment, the antibodies of the invention can be used to treat, ameliorate or prevent diseases, disorders or conditions, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of

diseases, disorders, or conditions includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

### **Type I and Type II Diabetes Mellitus**

[0238] In highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof, especially neutralizing or antagonistic antibodies) may be used to diagnose, prognose, treat, prevent, or ameliorate diabetes mellitus (type I and type II) as well as conditions associated with diabetes mellitus (type I and type II), including, but not limited to, diabetic ketoacidosis, diabetic coma, nonketotic hyperglycemic-hyperosmolar coma, seizures, mental confusion, drowsiness, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other cardiovascular diseases and disorders), dyslipidemia, kidney disease (e.g., renal failure, nephropathy other renal disorders), nerve damage, neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and infectious diseases, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture.

[0239] In highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to treat or prevent an insulin related disease, disorder, or condition. In specific embodiments, the compositions of the invention are administered to treat or prevent a disorder characterized by a state of insulin resistance. Disorders characterized by insulin resistance that may be treated (e.g., ameliorated), prevented, diagnosed, and/or prognosed using the compositions of the invention include, but are not limited to, NIDDM, obesity, hypertension, renal failure, androgen excess, and liver cirrhosis or liver disease, injury and/or complications associated with transplantation. In further, specific embodiments, the compositions of the invention are administered to treat or prevent hyperinsulinemia or a disorder or condition associated therewith.



[0240] In highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) may be used to diagnose, prognose, treat, prevent, or ameliorate diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells.

[0241] In other highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to an animal, preferably a mammal, and most preferably a human, in order to regulate the animal's weight. In specific embodiments, the antibodies, polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin. In still other embodiments the antibodies polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin-like growth factor.

[0242] In highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used to diagnose, treat, prevent, or prognose or monitor non-insulin dependent diabetes (NIDDM) or a condition associated with NIDDM.

[0243] In highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to treat or prevent non-insulin dependent diabetes (NIDDM) or a condition associated with NIDDM.

[0244] In other preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used to diagnose, treat, prevent, or prognose or monitor insulin dependent diabetes (IDDM) or a condition associated with IDDM.

[0245] In other preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to treat or prevent insulin dependent diabetes (IDDM) or a condition associated with IDDM.

[0246] In highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used to treat, prevent, ameliorate,

diagnose and/or prognose diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells. In other preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used to treat, prevent, ameliorate, diagnose and/or prognose diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells.

[0247] In other highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to regulate glucose metabolism. In highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to increase glucose metabolism.

[0248] In other highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used treat, prevent, ameliorate, diagnose and/or prognose hyperglycemia.

[0249] In other highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used to diagnose, treat, prevent, or prognose or monitor dyslipidemia or a condition associated with dyslipidemia.

[0250] Additionally, in highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used to diagnose, treat, prognose or monitor obesity.

[0251] In other highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to treat obesity or a condition associated with obesity.

[0252] In other highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to limit weight gain.

[0253] In other highly preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) to suppress appetite.

[0254] In other preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to increase appetite.

[0255] In other preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to alter or regulate nutritional partitioning in the patient. In one embodiment, the

antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered according to this method to reduce fat mass. In another embodiment, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered according to this method to increase muscle mass.

[0256] In other preferred embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to promote weight gain.

[0257] In other embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used to diagnose, treat, prevent, or prognose or monitor hypertension or a condition associated with hypertension.

[0258] In other embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used to diagnose, treat, prevent, or prognose or monitor coronary artery disease or a condition associated with coronary artery disease.

[0259] In other embodiments, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are used to diagnose, treat, prevent, or prognose or monitor a neuropathy, neural injury, or a condition associated with a neuropathy or neural injury. Neuropathies that can be diagnosed, treated, prevented, or prognosed using the compositions of the invention include, but are not limited to, autonomic neuropathy, parasympathetic neuropathy, and polyneuropathy. In preferred embodiments, the compositions of the invention are used to diagnose, treat, prevent, or prognose parasympathetic neuropathy or parasympathetic neural injury or conditions associated with parasympathetic neuropathy or parasympathetic neural injury. In highly preferred embodiments, the compositions of the invention are used to diagnose, treat, prevent, or prognose hepatic parasympathetic neuropathy or hepatic parasympathetic neural injury, and/or conditions associated with hepatic parasympathetic neuropathy or hepatic parasympathetic neural injury.

[0260] In one embodiment, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to increase glucose production in adipocytes and/or other cells.

[0261] Additionally, in one embodiment, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to increase gluconeogenesis in adipocytes and/or other cells.

[0262] In a highly preferred embodiment, the antibodies of the invention (including fragments, variants, and fusion proteins thereof) are administered to a patient (preferably a human) to modulate (e.g., increase) the effect of insulin on blood glucose levels.

[0263] A highly preferred embodiment of the invention is a method of increasing glucose uptake of a cell comprising contacting a cell with one or more GMAD polypeptides of the invention. A specific embodiment is this method performed *in vitro*. A specific embodiment is this method performed *in vivo*. A specific embodiment is where the cell is a liver cell, or where the cell is an adipocyte, or where the cell is a kidney cell, or where the cell is a muscle cell.

[0264] In one embodiment, the invention provides a method of increasing glucose production of a cell comprising contacting a cell with a GMAD antibody. In one embodiment, this method is performed *in vitro*. In another embodiment this method is performed *in vivo*. In specific embodiments, the cell contacted according to this method is a liver cell, an adipocyte, a kidney cell, or a muscle cell.

[0265] In another embodiment, the invention provides a method of decreasing glucose uptake by a cell comprising contacting a cell with a GMAD antibody of the invention (including fragments, variants, and fusion proteins as described herein). In one embodiment, this method is performed *in vitro*. In another embodiment this method is performed *in vivo*. In specific embodiments, the cell contacted according to this method is a liver cell, an adipocyte, a kidney cell, a skin cell, a bone cell, or a skeletal muscle cell.

[0266] In another embodiment, the invention provides a method of increasing the sensitivity of a cell to insulin comprising contacting a cell with a GMAD antibody of the invention (including fragments, variants, and fusion proteins as described herein). In one embodiment, this method is performed *in vitro*. In another embodiment this method is performed *in vivo*. In specific embodiments, the cell contacted according to this method is a liver cell, an adipocyte, a kidney cell, a skin cell, a bone cell, or a skeletal muscle cell.

[0267] In another highly preferred embodiment, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate cardiovascular disease.

[0268] In another highly preferred embodiment, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below),

diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious disease or disorder as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture).

[0269] In another highly preferred embodiment, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate obesity and/or complications associated with obesity.

[0270] In additional highly preferred embodiments, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate weight loss or alternatively, weight gain.

[0271] In additional highly preferred embodiments, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate complications associated with insulin resistance.

[0272] In additional highly preferred embodiments, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate complications associated with hyperglycemia.

[0273] In additional highly preferred embodiments, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate complications associated with obesity.

[0274] In additional preferred embodiments, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate Fragile X Syndrome.

[0275] In additional preferred embodiments, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.

[0276] In additional highly preferred embodiments, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver

disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas.

[0277] In additional preferred embodiments, the antibodies of the invention are used to treat, prevent, diagnose, or ameliorate liver disorders, including, but not limited to, cirrhosis, hepatoblastoma, hepatocarcinoma, jaundice, hepatitis, liver metabolic diseases, and conditions that are attributable to the differentiation of hepatocyte progenitor cells.

### **Endocrine Disorders**

[0278] In preferred embodiments, antibodies of the present invention, are used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

[0279] Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

[0280] Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

[0281] Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma—islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease,

Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

[0282] In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

[0283] Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

#### **Inflammation and Inflammatory Disorders**

[0284] In other embodiments, the antibodies of the invention (including fragments and variants thereof) may be used in the diagnosis, prognosis, prevention, and/or treatment of inflammatory disorders, as described herein.

[0285] In highly preferred embodiments, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, and/or diagnosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[0286] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, and/or diagnosed using antibodies of the invention. Moreover, these molecules can be used to treat, prevent,

and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[0287] Additionally, antibodies of the invention, may be used to treat or prevent IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

[0288] Moreover, antibodies of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to diagnose, prognose, prevent, and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1), respiratory disorders (such as, e.g., asthma and allergy); gastrointestinal disorders (such as, e.g., inflammatory bowel disease); cancers (such as, e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (such as, e.g., multiple sclerosis; ischemic brain injury and/or stroke; traumatic brain injury; neurodegenerative disorders, such as, e.g., Parkinson's disease and Alzheimer's disease; AIDS-related dementia; and prion disease); cardiovascular disorders (such as, e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (such as, e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogeneic transplant rejection).

[0289] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, antibodies of the invention have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adenitis, alveolitis, angiocholecystitis, appendicitis, balanitis,



blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chondritis, cochitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[0290] In specific embodiments, antibodies of the invention, are useful to treat, diagnose, and/or prevent organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[0291] In another specific embodiment, antibodies of the invention are used as an agent to induce higher affinity antibodies.

[0292] In another specific embodiment, antibodies of the invention are used as an agent to increase serum immunoglobulin concentrations.

### **Cardiovascular Disorders**

[0293] Antibodies of the invention may be used to treat cardiovascular disorders, including peripheral artery disease, such as limb ischemia.

[0294] Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart

defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilog of Fallot, ventricular heart septal defects.

[0295] Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

[0296] Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

[0297] Heart valve disease include aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

[0298] Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary

subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

[0299] Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

[0300] Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomas, bacillary angiomas, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, ataxia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

[0301] Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

[0302] Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

[0303] Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

[0304] Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

[0305] Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

[0306] Antibodies of the invention are especially effective for the treatment of critical limb ischemia and coronary disease.

[0307] Antibodies of the invention may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

#### **Additional Therapeutic Uses of Antibodies**

[0308] The present invention is directed to a method for inhibiting GMAD-mediated insulin resistance, which involves administering to a cell (which expresses a GMAD polypeptide *in vitro* or *in vivo*), an effective amount of an antibody of the invention, capable of decreasing GMAD mediated signaling (through a GMAD receptor). Preferably, GMAD mediated signaling is decreased to treat a disease wherein increased GMAD expression is exhibited.

[0309] The antibodies of the invention can be used to treat, ameliorate or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of GMAD, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or

conditions associated with aberrant GMAD expression and/or activity includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0310] Further, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which inhibit GMAD-mediated biological activities (e.g., the inhibition of insulin action) can be administered to an animal to treat, prevent or ameliorate a disease or disorder described herein, particularly Type I and II Diabetes Mellitus and inflammatory disorders. These antibodies may diminish either all or a subset of the biological activities of GMAD, for example, by inducing a conformational change in GMAD. In a specific embodiment, an antibody of the present invention that inhibits GMAD activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, at least two-fold, at least three-fold, at least four fold, at least five fold, at least ten-fold, at least twenty-fold, at least fifty-fold, or at least one hundred-fold relative to GMAD activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments and/or antibody variants that inhibit GMAD activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, at least two-fold, at least three-fold, at least four fold, at least five fold, at least ten-fold, at least twenty-fold, at least fifty-fold, or at least one hundred-fold relative to GMAD activity in absence of the said antibodies or antibody fragments and/or antibody variants is administered to an animal to treat, prevent or ameliorate a disease or disorder.

[0311] Further, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which inhibit GMAD-mediated biological activities (e.g., the inhibition of insulin action) can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, excess or aberrant GMAD function, or aberrant GMAD

receptor expression. These antibodies may diminish either all or a subset of the biological activities of GMAD, for example, by preventing GMAD interaction with its receptor. In a specific embodiment, an antibody of the present invention that diminishes GMAD activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, at least two-fold, at least three-fold, at least four fold, at least five fold, at least ten-fold, at least twenty-fold, at least fifty-fold, or at least one hundred-fold relative to GMAD activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, excess GMAD function, or aberrant GMAD receptor expression. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments and/or antibody variants that diminish GMAD activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, at least two-fold, at least three-fold, at least four fold, at least five fold, at least ten-fold, at least twenty-fold, at least fifty-fold, or at least one hundred-fold relative to GMAD activity in absence of the said antibodies or antibody fragments and/or antibody variants is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression or excess GMAD function or aberrant GMAD receptor expression.

[0312] Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that function as agonists or antagonists of GMAD, preferably of GMAD signal transduction, can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, lack of GMAD function, or aberrant GMAD receptor expression. For example, antibodies of the invention that act as GMAD agonists may be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, lack of GMAD function, or aberrant GMAD receptor expression. As an alternative example, antibodies of the invention which disrupt or prevent the interaction between GMAD and its receptor or inhibit, reduce, or prevent signal transduction through one or more GMADs, may be administered to an animal to

treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, lack of GMAD function, or aberrant GMAD receptor expression. Antibodies of the invention which do not prevent GMAD from binding its receptor but inhibit or downregulate GMAD signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, lack of GMAD function or aberrant GMAD receptor expression. The ability of an antibody of the invention to enhance, inhibit, upregulate or downregulate GMAD signal transduction may be determined by techniques described herein or otherwise known in the art. For example, GMAD-induced receptor activation and the activation of signaling molecules can be determined by detecting the association of adaptor proteins with the GMAD receptors, by immunoprecipitation followed by western blot analysis (for example, as described herein).

[0313] Further, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which activate GMAD-mediated biological activities (e.g., the inhibition of insulin action) can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, or aberrant GMAD receptor expression. These antibodies may potentiate or activate either all or a subset of the biological activities of GMAD, for example, by inducing a conformational change in GMAD. In a specific embodiment, an antibody of the present invention that increases GMAD activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, at least two-fold, at least three-fold, at least four fold, at least five fold, at least ten-fold, at least twenty-fold, at least fifty-fold, or at least one hundred-fold relative to GMAD activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, lack of GMAD function, or aberrant GMAD receptor expression. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments and/or antibody variants that increase GMAD activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at

least 95%, at least 99%, at least two-fold, at least three-fold, at least four fold, at least five fold, at least ten-fold, at least twenty-fold, at least fifty-fold, or at least one hundred-fold relative to GMAD activity in absence of the said antibodies or antibody fragments and/or antibody variants is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression or lack of GMAD function or aberrant GMAD receptor expression.

[0314] In a specific embodiment, an antibody of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that inhibits or downregulates, in full or in part, GMAD activity (e.g., inhibition of insulin action) by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to GMAD activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, excessive GMAD function, aberrant GMAD receptor expression, or excessive GMAD receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments, and/or variants that inhibit or downregulate GMAD activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, at least 50%, at least 45%, at least 40%, at least 45%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to GMAD activity in absence of said antibodies, antibody fragments, and/or antibody variants are administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant GMAD expression, excessive GMAD function, aberrant GMAD receptor expression, or excessive GMAD receptor function.

#### **Therapeutic/Prophylactic Compositions and Administration**

[0315] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of antibody (or fragment or variant thereof) or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, an antibody or fragment or variant thereof is substantially purified (*i.e.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to, animals



such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably a human.

[0316] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0317] Various delivery systems are known and can be used to administer an antibody of the invention or a fragment or variant thereof, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or antibody fragment, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0318] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0319] In another embodiment, the composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1535 (1990); Treat *et al.*, in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 3 17-327; see generally *ibid.*).

[0320] In yet another embodiment, the composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:20 1 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:71 (1983); see also Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:35 1 (1989); Howard *et al.*, *J. Neurosurg.* 7 1:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, *i.e.*, the brain, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

[0321] Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1535 (1990)).

[0322] In a specific embodiment where the composition of the invention is a nucleic acid encoding an antibody, the nucleic acid can be administered *in vivo* to promote expression of its encoded antibody, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see *e.g.*, Joliot *et al.*, *Proc. Natl. Acad. Sci. USA* 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0323] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of an antibody or a fragment

thereof, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the antibody or fragment thereof, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0324] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating

the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0325] The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0326] The amount of the composition of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0327] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of therapeutic or pharmaceutical compositions of the invention may be reduced by enhancing uptake and tissue penetration (*e.g.*, into the brain) of the antibodies by modifications such as, for example, lipidation.

[0328] Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments, or variants,

(e.g., derivatives), or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0329] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to one or more GMAD polypeptides, or polynucleotides encoding antibodies that specifically bind to one or more GMAD polypeptides, for both immunoassays and therapy of disorders related to GMAD polynucleotides or polypeptides, including fragments thereof. Such antibodies will preferably have an affinity for GMAD polypeptides and/or GMAD polypeptide fragments. Preferred binding affinities include those with a dissociation constant or  $K_D$  of less than or equal to  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M, or  $10^{-5}$  M. More preferably, antibodies of the invention bind GMAD polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M, or  $10^{-8}$  M. Even more preferably, antibodies of the invention bind GMAD polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M. In a preferred embodiment, antibodies of the invention inhibit proliferation, differentiation, and/or apoptosis of GMAD receptor expressing cells. In an additional preferred embodiment, antibodies of the invention induce differentiation of GMAD receptor expressing cells.

[0330] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

[0331] The antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic agents, including but not limited to anti-diabetic agents, chemotherapeutic agents, antibiotics, antivirals, anti-

retroviral agents, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents and cytokines. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

**Combination Therapies with anti-GMAD antibodies, anti-diabetic drugs, and/or Immunomodulatory agents,**

[0332] Anti-GMAD antibodies may be administered in combination with other anti-GMAD antibodies, GMAD, and/or anti-diabetic drugs.

[0333] In specific embodiments, an antibody of the invention that specifically binds GMAD is used or administered in combination with a second antibody that specifically binds GMAD. In another embodiment, the antibodies specific for GMAD are antagonistic antibodies that inhibit GMAD secretion and/or GMAD biological activity (e.g., inhibition of insulin action, inhibition of glucose uptake). In a specific embodiment, the combination of anti-GMAD treatment inhibits more GMAD biological activity than either anti-GMAD antibody treatment alone.

[0334] In another embodiment, the antibodies specific for GMAD are agonistic antibodies that stimulate cellular insulin resistance. In a specific embodiment, the combination of anti-GMAD treatment stimulates more insulin resistance than either anti-GMAD antibody treatment alone. The anti-GMAD antibodies can be administered either simultaneously, sequentially, or a combination of simultaneous or sequential administration throughout the dosage regimen. In another specific embodiment anti-GMAD antibodies are used or administered in combination with a chemotherapeutic drug, antidiabetic drug, and/or immunomodulatory drug. In a particular embodiment, the synergistic inhibition of insulin resistance from anti-GMAD antibody treatment, is more evident or more pronounced when the anti-GMAD antibodies are used or administered in combination with an antidiabetic drug, a chemotherapeutic agent, immunomodulatory drug, and/or a cross-linking reagent.

[0335] In one embodiment, the compositions of the invention are administered in combination with other antidiabetic drugs, including, but not limited to Thiazolidinediones, or TZDs including but not limited to, rosiglitazone, pioglitazone, and troglitazone. In another specific embodiment, compositions of the invention are used in combination with oral hypoglycemic sulfonylurea drugs including, but not limited to, acarbose, acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, metformin, tolazamide, and/or tolbutamide. In another specific embodiment, compositions of the invention are used in combination with insulin, insulin derivatives, and/or insulin substitutes. In still other embodiments, compositions of the invention are administered in combination with one or more of the following, Acenorm™; Acenorm™ Cor™; Acepress™; Acepril™; Aceten™; Adacor™; Alopresin™; Angiopril™; Apuzin™; Asisten™; Capace™; Capoten™; Capotena™; Capril™; Captensin™; Captoflux™; Captolane™; Captoplong™; Captopress™; Captopril™; Captoprilan™; Captoril™; Captral™; Cardipril™; Cesplon™; Cryopril™; Debax™; Dexacap™; Ecapres™; Ecaten™; Epicordin™; Epsitron™; Farcopril™; Farmoten™; Hiperil™; Hypotensor™; Inhibace™; Isopresol™; Katopil™; Lopirin™; Lopril™; Medepres™; Mereprine™; Minitent™; Praten™; Precaptil™; Rilcapton™; Ropril™; Smarten™; Tensicap™; Tensiomen™; Tensobon™; Tenzib™; and Zorkaptil™. In still other embodiments, compositions of the invention are administered in combination with one or more of the following: a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent.

[0336] In other embodiments, antibody compositions of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICLOVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF).

[0337] In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with steroids, cyclosporine, cyclosporine

analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the compositions of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate mofetil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrexate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

[0338] In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, *N*-acetamidocaproic acid, *S*-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

#### **Additional Combination Therapies**

[0339] The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be administered alone or in combination with other therapeutic or prophylactic regimens (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy, anti-tumor agents, anti-angiogenesis and anti-inflammatory agents). Such combinatorial therapy may be administered sequentially and/or concomitantly.



[0340] The invention also encompasses combining the polynucleotides and/or antibodies of the invention with other proposed or conventional diabetic therapies. Thus, for example, the polynucleotides and/or antibodies of the invention can be combined with compounds that singly exhibit insulin stimulatory effects, and or glucose-transport action.

[0341] The antibodies and/or antibody compositions of the invention and/or agonists or antagonists thereof is administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those techniques further discussed herein.

[0342] In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-angiogenic agent(s). Anti-angiogenic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals. Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0343] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates. Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium

molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0344] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., *Cancer Res.* 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d, L-3,4-dehydropoline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., *J. Bio. Chem.* 267:17321-17326, 1992); Chymostatin (Tomkinson et al., *Biochem J.* 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., *Nature* 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, *J. Clin. Invest.* 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., *J. Biol. Chem.* 262(4):1659-1664, 1987); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., *Agents Actions* 36:312-316, 1992); and metalloproteinase inhibitors such as BB94.

[0345] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC359555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839);

Octreotide (Somatostatin); Panretin; Penicillamine; Photopoint; PI-88; Prinomastat (AG-3540) Purlitin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

[0346] Anti-angiogenic agents that may be administered in combination with the antibodies and/or the compositions of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, AG-3540 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, EMD-121974 (Merck KgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

[0347] In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the antibody and antibody compositions of the invention

include, but are not limited to, amoxicillin, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

[0348] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with steroid therapy. Steroids that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, oral corticosteroids, prednisone, and methylprednisolone (e.g., IV methylprednisolone). In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with prednisone.

[0349] The antibodies and antibody compositions of the invention may be administered alone or in combination with other adjuvants. Adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with alum. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis, and/or PNEUMOVAX-23™. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same

individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0350] In another specific embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated therewith. In one embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose any Gram positive bacterial infection and/or any disease, disorder, and/or condition associated therewith. In another embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more members of the genus *Enterococcus* and/or the genus *Streptococcus*. In another embodiment, antibody and antibody compositions of the invention are used in any combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more members of the Group B streptococci. In another embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with *Streptococcus pneumoniae*.

[0351] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with CD40 ligand (CD40L), a soluble form of CD40L (e.g., AVREND™), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

[0352] In a nonexclusive embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five, ten, or more of the following drugs: NRD-101 (Hoechst Marion Roussel), diclofenac (Dimethaid), oxaprozin potassium (Monsanto), mecamermin (Chiron), T-714 (Toyama), pemetrexed disodium (Eli Lilly), atreleuton (Abbott), valdecoxib (Monsanto), eltenac (Byk Gulden), campath, AGM-1470 (Takeda), CDP-571 (Celltech Chiroscience), CM-101 (CarboMed), ML-3000 (Merckle), CB-2431 (KS Biomedix), CBF-BS2 (KS Biomedix), IL-1Ra gene therapy (Valentis), JTE-522 (Japan Tobacco), paclitaxel (Angiotech), DW-166HC (Dong

Wha), darbufelone mesylate (Warner-Lambert), soluble TNF receptor 1 (synergen; Amgen), IPR-6001 (Institute for Pharmaceutical Research), trocade (Hoffman-La Roche), EF-5 (Scotia Pharmaceuticals), BIIL-284 (Boehringer Ingelheim), BIIF-1149 (Boehringer Ingelheim), LeukoVax (Inflammatics), MK-671 (Merck), ST-1482 (Sigma-Tau), and butixocort propionate (WarnerLambert).

[0353] In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five or more of the following drugs: methotrexate, sulfasalazine, sodium aurothiomalate, auranofin, cyclosporine, penicillamine, azathioprine, an antimalarial drug, cyclophosphamide, chlorambucil, gold, ENBREL™ (Etanercept), anti-TNF antibody, LJP 394 (La Jolla Pharmaceutical Company, San Diego, California) and prednisolone.

[0354] In an additional embodiment, antibody and antibody compositions of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the antibody and antibody compositions of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[0355] In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with other polypeptides, polynucleotides or antibodies used to treat diagnose or ameliorate diabetes, including, but not limited to RELM and/or other FIZZ family polypeptides, Apo-lipoprotein, Insulin, Interferon Alpha, M-CSF, Platelet factor 4, IL-2, Resistin, AC2 Inhibitor, Leptin, IL-1 Receptor Agonist, HLD0U18, HCE-IP80, GLP-1, ABC1, Adiposin, CNTF, CTLA4, Decorin, GGF-2, Glucagon, IL-10, IL2-Diphtheria Toxin Chimera, IL-4, Microsomal Transfer Protein, NGF, NT-3, PAF acetyl hydrolase, PDGF, Prosaptide, TGF Beta 2, Troponin 1, Lp-PLA2, Fas, FasL, TR6, HNHFE71, HLWCF05, Preproapolipoprotein, BMP-1, BMP-2B, BMP-4, BMP-5, BMP-6, Osteogenic protein-2, GDF-1, BMP-9, BMP-10, BMP-12, BMP-15, BMP-17, BMP-18, APM-1, ACRP-30, Calpain 10a, Calpain-10b, Calpain-10c, and VEGF-1.

**Demonstration of Therapeutic or Prophylactic Utility of a Composition**

[0356] The compounds of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays which can be used to determine whether administration of a specific antibody or composition of the present invention is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered an antibody or composition of the present invention, and the effect of such an antibody or composition of the present invention upon the tissue sample is observed. In various specific embodiments, *in vitro* assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if an antibody or composition of the present invention has a desired effect upon such cell types. Preferably, the antibodies or compositions of the invention are also tested in *in vitro* assays and animal model systems prior to administration to humans (See, e.g., Examples 6 and 9).

[0357] Antibodies or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal model systems, including but not limited to rats, mice, chicken, cows, monkeys, and rabbits. For *in vivo* testing of an antibody or composition's toxicity any animal model system known in the art may be used.

[0358] Antibodies or compositions of the invention can be tested for their ability to reduce tumor formation in *in vitro*, *ex vivo* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to inhibit viral replication or reduce viral load in *in vitro* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to reduce bacterial numbers in *in vitro* and *in vivo* assays known to those of skill in the art. Antibodies or compositions of the invention can also be tested for their ability to alleviate one or more symptoms associated with diabetes (e.g., insulin resistance). Antibodies or compositions of the invention can also be tested for their ability to decrease the time course of the infectious disease. Further, antibodies or compositions of the invention can be tested for their ability to increase the survival period of animals suffering from disease or disorder, including cancer, an immune disorder or an infectious disease. Techniques known to those of skill in the art can be used to analyze the function of the antibodies or compositions of the invention *in vivo*.

[0359] Antigen expression can be assayed, for example, by immunoassays including, but not limited to, competitive and non-competitive assay systems using techniques such as western blots, immunohistochemistry radioimmunoassays, ELISA

(enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays and FACS analysis. The activation of signaling molecules can be assayed, for example, by kinase assays and electrophoretic shift assays (EMSAs). In a preferred embodiment, the ability of an antibody or composition of the invention to induce B-cell proliferation is measured. In another preferred embodiment, the ability of an antibody or composition of the invention to modulate immunoglobulin expression is measured.

#### **Panels/Mixtures**

[0360] The present invention also provides for mixtures of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to GMAD or a fragment or variant thereof, wherein the mixture has at least one, two, three, four, five or more different antibodies of the invention. In specific embodiments, the invention provides mixtures of at least 2, preferably at least 4, at least 6, at least 8, at least 10, at least 12, at least 15, at least 20, or at least 25 different antibodies that specifically bind to GMAD or fragments or variants thereof, wherein at least 1, at least 2, at least 4, at least 6, or at least 10, antibodies of the mixture is an antibody of the invention. In a specific embodiment, each antibody of the mixture is an antibody of the invention.

[0361] The present invention also provides for panels of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to GMAD or a fragment or variant thereof, wherein the panel has at least one, two, three, four, five or more different antibodies of the invention. In specific embodiments, the invention provides for panels of antibodies that have different affinities for GMAD, different specificities for GMAD, or different dissociation rates. The invention provides panels of at least 10, preferably at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, at least 950, or at least 1000, antibodies. Panels of antibodies can be used, for example, in 96 well plates for assays such as ELISAs.



[0362] The present invention further provides for compositions comprising, one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains of a heavy chain of one or more of the scFvs referred to in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s of a heavy chain of one or more of the scFvs referred to in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s of a heavy chain of one or more of the scFvs referred to in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s as of a heavy chain of one or more of the scFvs referred to in Table 1, or a variant thereof.

[0363] Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains of a light chain of one or more of the scFvs referred to in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s domains of a light chain of one or more of the scFvs referred to in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s of a light chain of one or more of the scFvs referred to in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention

comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s domains of a light chain of one or more of the scFvs referred to in Table 1, or a variant thereof.

#### Kits

[0364] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[0365] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In an alternative embodiment, a kit comprises an antibody fragment that specifically binds to GMAD polypeptides or fragments or variants thereof. In a specific embodiment, the kits of the present invention contain a substantially isolated GMAD polypeptide or fragment or variant thereof as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with any, some or all GMAD. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to GMAD polypeptides (*e.g.*, the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized GMAD. The GMAD provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above-described kit includes a solid support to which GMAD is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to GMAD can be detected by binding of the said reporter-labeled antibody.

[0366] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with GMAD,

and means for detecting the binding of GMAD polypeptides to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0367] In one diagnostic configuration, test serum is reacted with a solid phase reagent having surface-bound GMAD obtained by the methods of the present invention. After GMAD polypeptides bind to a specific antibody, the unbound serum components are removed by washing, reporter-labeled anti-human antibody is added, unbound anti-human antibody is removed by washing, and a reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-GMAD antibody on the solid support. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate.

[0368] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0369] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant GMAD, and a reporter-labeled anti-human antibody for detecting surface-bound anti-GMAD antibody.

### **Gene Therapy**

[0370] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of GMAD and/or its receptors, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this

embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0371] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0372] For general reviews of the methods of gene therapy, see Goldspiel *et al.*, Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[0373] In a preferred aspect, a composition of the invention comprises, or alternatively consists of, nucleic acids encoding an antibody, said nucleic acids being part of an expression vector that expresses the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acids have promoters, preferably heterologous promoters, operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra *et al.*, Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is an scFv; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments or variants thereof, of an antibody.

[0374] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

[0375] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be

accomplished by any of numerous methods known in the art, *e.g.*, by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, *e.g.*, by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, *e.g.*, PCT Publications WO 92/06 180; WO 92/22715; W092/203 16; W093/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra *et al.*, Nature 342:435-438 (1989)).

[0376] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention or fragments or variants thereof are used. For example, a retroviral vector can be used (see Miller *et al.*, Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen *et al.*, Biotherapy 6:29 1-302 (1994), which describes the use of a retroviral vector to deliver the *mdr 1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes *et al.*, J. Clin. Invest. 93:644-651(1994); Klein *et al.*, Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

[0377] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout *et al.*, *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld *et al.*, *Science* 252:431-434 (1991); Rosenfeld *et al.*, *Cell* 68:143-155 (1992); Mastrangeli *et al.*, *J. Clin. Invest.* 91:225-234 (1993); PCT Publication W094/12649; and Wang, *et al.*, *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0378] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh *et al.*, *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

[0379] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[0380] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, *e.g.*, Loeffler and Behr, *Meth. Enzymol.* 217:599-718 (1993); Cohen *et al.*, *Meth. Enzymol.* 217:718-644 (1993); *Clin. Pharma. Ther.* 29:69-92m (1985)) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of

the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0381] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (*e.g.*, hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[0382] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, *e.g.*, as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[0383] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[0384] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody or fragment thereof are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see *e.g.* PCT Publication WO 94/08598; Stemple and Anderson, *Cell* 71:973-985 (1992); Rheinwald, *Meth. Cell Bio.* 21A:229 (1980); and Pittelkow and Scott, *Mayo Clinic Proc.* 71:771 (1986)).

[0385] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

## Examples

### Example 1: Isolation of scFvs that specifically bind GMAD

#### General Methods

##### Rescue of the library.

[0386] A library of scFvs is constructed from the RNA of human PBLs as described in WO92/01047 (which is hereby incorporated by reference in its entirety). To rescue phage displaying antibody fragments, approximately  $10^9$  *E. coli* harboring the phagemid are used to inoculate 50 ml of 2x TY containing 1% glucose and 100 micrograms/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU,  $2 \times 10^8$  TU of delta gene 3 helper (M13 delta gene III, see WO92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2x TY containing 100 micrograms/ml ampicillin and 50 micrograms/ml kanamycin and grown overnight. Phage are prepared as described in WO92/01047.

[0387] M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37°C without shaking and then for a further hour at 37°C with shaking. Cells were spun down (IEC-Centra 8, 4000 revs/min for 10 min), resuspended in 300 ml 2x TY broth containing 100 micrograms ampicillin/ml and 25 micrograms kanamycin/ml (2x TY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 micrometer filter (Minisart NML; Sartorius) to give a final concentration of approximately  $10^{13}$  transducing units/ml (ampicillin-resistant clones).

##### Panning the Library.

[0388] Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 micrograms/ml or 10 micrograms/ml of a polypeptide of the present invention. Tubes are



blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately  $10^{13}$  TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log *E. coli* TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The *E. coli* are then plated on TYE plates containing 1% glucose and 100 micrograms/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is usually repeated for a total of 2-4 rounds of affinity purification.

#### Characterization of Binders.

[0389] Eluted phage from the final rounds of selection are used to infect *E. coli* HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtiter plates coated with either 10 picograms/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see e.g., WO92/01047) and then by sequencing.

#### Isolation of scFvs referred to in Table 1

[0390] The scFvs presented in Table 1 were isolated using a methods similar to those described above. Briefly, Flag-tagged recombinant human GMAD was immobilized in Immuno tubes. Three phage display libraries from Cambridge Antibody Technology (Cambridgeshire, United Kingdom) were screened for GMAD binding scFvs. Prior to panning the phage libraries on FLAG tagged GMAD, the phage libraries were each incubated with Flag peptide (SEQ ID NO:39) for deselection. Three rounds of selection for phage expressing scFv that bind GMAD were performed by panning the phage libraries on flag-tagged GMAD.

[0391] After the first and second round of panning, bound phages were eluted and amplified in *E. coli* for the subsequent pannings. After round two of panning, four 96-well plates of single bacterial colonies (each infected with an scFv expressing phage particle)

were isolated and grown. Similarly, eight 96-well plates of single bacterial colonies were isolated and grown up after round three of panning. The scFvs contained in each of the bacterial colonies were then sequenced. Certain of the scFvs had identical sequences, so a panel of phage expressing unique scFv sequences was created and further characterized.

[0392] The individual phage isolates in the panel of phage, each phage expressing a unique scFv that bound to flag-tagged GMAD, were tested to ensure specificity for GMAD using an ELISA assay. The scFvs were tested in an ELISA for their ability to bind a heterologous flag-tagged protein, in this case - immobilized soluble TL3 (amino acids 105-251 of SEQ ID NO:234, GenBank Accession Number NP\_003799, also described in International Patent Application Publication Number WO97/33902 and WO2001/96528 which are herein incorporated by reference in their entireties). ScFvs specific for GMAD (i.e., that bind flag tagged GMAD but not flagged tagged TL-3 and/or flag-tagged TR2) in this ELISA assay were identified and resequenced for confirmation. The scFvs that specifically bind GMAD identified in this manner are listed in Table 1 and the sequences of these scFvs are shown in SEQ ID NOS:40-136 (amino acid sequences) and SEQ ID NOS: 136-233 (nucleotide sequences).

#### **Example 2: Identification and Cloning of VH and VL domains**

[0393] One method to identify and clone VH and VL domains from cell lines expressing a particular antibody is to perform PCR with VH and VL specific primers on cDNA made from the antibody expressing cell lines. Briefly, RNA is isolated from the cell lines and used as a template for RT-PCR designed to amplify the VH and VL domains of the antibodies of the EBV cell lines. Cells may be lysed in the TRIzol® reagent (Life Technologies, Rockville, MD) and extracted with one fifth volume of chloroform. After addition of chloroform, the solution is allowed to incubate at room temperature for 10 minutes, and then centrifuged at 14,000 rpm for 15 minutes at 4°C in a tabletop centrifuge. The supernatant is collected and RNA is precipitated using an equal volume of isopropanol. Precipitated RNA is pelleted by centrifuging at 14,000 rpm for 15 minutes at 4°C in a tabletop centrifuge. Following centrifugation, the supernatant is discarded and washed with 75% ethanol. Following washing, the RNA is centrifuged again at 800 rpm for 5 minutes at 4°C. The supernatant is discarded and the pellet allowed to air dry. RNA is then dissolved in DEPC water and heated to 60°C for 10 minutes. Quantities of RNA can be determined using optical density measurements.

[0394] cDNA may be synthesized, according to methods well-known in the art, from 1.5-2.5 micrograms of RNA using reverse transcriptase and random hexamer primers. cDNA is then used as a template for PCR amplification of VH and VL domains. Primers used to amplify VH and VL genes are shown in Table 8. Typically a PCR reaction makes use of a single 5' primer and a single 3' primer. Sometimes, when the amount of available RNA template is limiting, or for greater efficiency, groups of 5' and/or 3' primers may be used. For example, sometimes all five VH-5' primers and all JH3' primers are used in a single PCR reaction. The PCR reaction is carried out in a 50 microliter volume containing 1X PCR buffer, 2mM of each dNTP, 0.7 units of High Fidelity Taq polymerase, 5' primer mix, 3' primer mix and 7.5 microliters of cDNA. The 5' and 3' primer mix of both VH and VL can be made by pooling together 22 pmole and 28 pmole, respectively, of each of the individual primers. PCR conditions are: 96°C for 5 minutes; followed by 25 cycles of 94°C for 1 minute, 50°C for 1 minute, and 72°C for 1 minute; followed by an extension cycle of 72°C for 10 minutes. After the reaction is completed, sample tubes were stored 4°C.

**Table 6: Primer Sequences Used to Amplify VH and VL domains.**

<b>Primer name</b>	<b>SEQ ID NO</b>	<b>Primer Sequence (5'-3')</b>
<b>VH Primers</b>		
Hu VH1-5'	3	CAGGTGCAGCTGGTGCAGTCTGG
Hu VH2-5'	4	CAGGTCAACTTAAGGGAGTCTGG
Hu VH3-5'	5	GAGGTGCAGCTGGTGGAGTCTGG
Hu VH4-5'	6	CAGGTGCAGCTGCAGGAGTCGGG
Hu VH5-5'	7	GAGGTGCAGCTGTTGCAGTCTGC
Hu VH6-5'	8	CAGGTACAGCTGCAGCAGTCAGG
Hu JH1,2-5'	9	TGAGGAGACGGTGACCAAGGGTGCC
Hu JH3-5'	10	TGAAGAGACGGTGACCAATTGTCCC
Hu JH4,5-5'	11	TGAGGAGACGGTGACCAAGGGTTCC
Hu JH6-5'	12	TGAGGAGACGGTGACCGTGGTCCC
<b>VL Primers</b>		
Hu Vkappa1-5'	13	GACATCCAGATGACCCAGTCTCC
Hu Vkappa2a-5'	14	GATGTTGTGATGACTCAGTCTCC
Hu Vkappa2b-5'	15	GATATTGTGATGACTCAGTCTCC
Hu Vkappa3-5'	16	GAAATTGTGTTGACGCAGTCTCC
Hu Vkappa4-5'	17	GACATCGTGATGACCCAGTCTCC
Hu Vkappa5-5'	18	GAAACGACACTCACGCAGTCTCC
Hu Vkappa6-5'	19	GAAATTGTGCTGACTCAGTCTCC
Hu Vlambda1-5'	20	CAGTCTGTGTTGACGCAGCCGCC
Hu Vlambda2-5'	21	CAGTCTGCCCTGACTCAGCCTGC
Hu Vlambda3-5'	22	TCCTATGTGCTGACTCAGCCACC
Hu Vlambda3b-5'	23	TCTTCTGAGCTGACTCAGGACCC
Hu Vlambda4-5'	24	CACGTTATACTGACTCAACCGCC
Hu Vlambda5-5'	25	CAGGCTGTGCTCACTCAGCCGTC
Hu Vlambda6-5'	26	AATTTTATGCTGACTCAGCCCCA
Hu Jkappa1-3'	27	ACGTTTGATTTCCACCTTGGTCCC
Hu Jkappa2-3'	28	ACGTTTGATCTCCAGCTTGGTCCC
Hu Jkappa3-3'	29	ACGTTTGATATCCACTTTGGTCCC
Hu Jkappa4-3'	30	ACGTTTGATCTCCACCTTGGTCCC
Hu Jkappa5-3'	31	ACGTTTAATCTCCAGTCGTGTCCC
Hu Jlambda1-3'	32	CAGTCTGTGTTGACGCAGCCGCC
Hu Jlambda2-3'	33	CAGTCTGCCCTGACTCAGCCTGC
Hu Jlambda3-3'	34	TCCTATGTGCTGACTCAGCCACC
Hu Jlambda3b-3'	35	TCTTCTGAGCTGACTCAGGACCC
Hu Jlambda4-3'	36	CACGTTATACTGACTCAACCGCC
Hu Jlambda5-3'	37	CAGGCTGTGCTCACTCAGCCGTC
Hu Jlambda6-3'	38	AATTTTATGCTGACTCAGCCCCA

[0395] PCR samples are then electrophoresed on a 1.3% agarose gel. DNA bands of the expected sizes (~506 base pairs for VH domains, and 344 base pairs for VL domains) can be cut out of the gel and purified using methods well known in the art. Purified PCR products can be ligated into a PCR cloning vector (TA vector from Invitrogen Inc., Carlsbad, CA). Individual cloned PCR products can be isolated after

transfection of *E. coli* and blue/white color selection. Cloned PCR products may then be sequenced using methods commonly known in the art.

**Example 3: [<sup>3</sup>H]-2-Deoxyglucose Uptake Assay.**

[0396] Adipose, skeletal muscle, and liver are insulin-sensitive tissues. Insulin can stimulate glucose uptake/transport into these tissues. In the case of adipose and skeletal muscle, insulin initiates the signal transduction that eventually leads to the translocation of the glucose transporter 4 molecule, GLUT4, from a specialized intracellular compartment to the cell surface. Once on the cell surface, GLUT4 allows for glucose uptake/transport.

[0397] A number of adipose and muscle related cell-lines can be used to test for glucose uptake/transport activity in the absence or presence of a combination of any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus. In particular, the 3T3-L1 murine fibroblast cells and the L6 murine skeletal muscle cells can be differentiated into 3T3-L1 adipocytes and into myotubes, respectively, to serve as appropriate *in vitro* models for the [<sup>3</sup>H]-2-deoxyglucose uptake assay (Garcia de Herreros et al., J. Biol. Chem. 264(33):19994-19999 (1989); Urso et al., J Biol Chem, 274(43): 30864-73 (1999); Wang et al., J Mol Endocrinol, 19(3): 241-8 (1997); Haspel et al., J Membr Biol, 169 (1): 45-53 (1999); Tsakiridis et al., Endocrinology, 136(10): 4315-22 (1995)).

**Differentiation of 3T3L-1**

[0398] Murine 3T3-L1 fibroblast are induced to differentiate into adipocytes according to the protocol described in Garcia de Herreros et al., J. Biol. Chem. 264(33):19994-19999 (1989) which is hereby incorporated by reference in its entirety. Alternatively, human adipocytes can be purchased from Zen-Bio, INC (# SA-1096).

**[<sup>3</sup>H]-2-Deoxyglucose Uptake**

[0399] Briefly,  $2 \times 10^5$  cells/100  $\mu$ L of adipocytes or differentiated 3T3-L1 cells are transferred to 96-well Tissue-Culture, "TC", treated, i.e., coated with 50 microgramr/mL of poly-L-lysine, plates in (DMEM + 10% FBS) and are incubated overnight at 37 °C in 5% CO<sub>2</sub>. The cells are first washed once with serum free low glucose DMEM medium and are then placed into 100 microliter/well of the same serum free low glucose DMEM medium containing anti-GMAD antibodies of the invention, and/or fragments

and variants thereof (e.g. 250ng/ml, 500 ng/ml or 1microgram/ml), for 16 hours at 37 °C in the absence or presence GMAD (e.g., 500 ng/ microliter). The plates are then washed three times with HEPES buffered saline. Insulin is added at 1-100 nM in HEPES buffered saline for 30 min at 37 °C. The cells are again washed three times with HEPES buffered saline. 10  $\mu$ M labeled [ $^3$ H]-2-deoxyglucose (Amersham, #TRK672) and 10  $\mu$ M unlabeled 2-deoxyglucose (SIGMA, D-3179) are added and allowed to incubate at room temperature for 10 minutes. Next, the cells are washed three times in cold PBS. As controls, the same conditions are carried out except in the absence of insulin or GMAD. The cells are lysed upon the addition of 150 microliter/well of 0.2 N NaOH and subsequent incubation with shaking for 20 minutes at room temperature. Samples are then transferred to a scintillation vial to which is added 5 mL of scintillation fluid. The vials are counted in a Beta-Scintillation counter. Uptake in duplicate conditions, the difference being the absence or presence of insulin, is determined with the following equation: 
$$\frac{[(\text{Insulin counts per minute "cpm"} - \text{Non-Specific cpm}) / (\text{No Insulin cpm} - \text{Non-Specific cpm})]}{}$$
 Non-specific uptake was measured in the presence of 10 micromolar cytochalasin B (SIGMA, C6762). Average responses fall within the limits of about 5-fold and 3-fold that of controls for adipocytes and myotubes, respectively.

#### **Example 4: Assaying for Glycosuria.**

[0400] Glycosuria (i.e., excess sugar in the urine), can be readily assayed to provide an index of the disease state of diabetes mellitus. Excess sugar in the urine of a patient as compared with a normal patient is symptomatic of IDDM and NIDDM. Efficacy of treatment of such a patient having IDDM and NIDDM is indicated by a resulting decrease in the amount of excess glucose in the urine. In a preferred embodiment for IDDM and NIDDM monitoring, urine samples from patients are assayed for the presence of glucose using techniques known in the art. Glycosuria in humans is defined by a urinary glucose concentration exceeding 100 mg per 100 ml. Excess sugar levels in those patients exhibiting glycosuria can be measured even more precisely by obtaining blood samples and assaying serum glucose.

#### **Example 5: Occurrence of Diabetes in NOD Mice.**

[0401] Female NOD (non-obese diabetic) mice are characterized by displaying IDDM with a course which is similar to that found in humans, although the disease is

more pronounced in female than male NOD mice. Hereinafter, unless otherwise stated, the term "NOD mouse" refers to a female NOD mouse. NOD mice have a progressive destruction of beta cells which is caused by a chronic autoimmune disease. Thus, NOD mice begin life with euglycemia, or normal blood glucose levels. By about 15 to 16 weeks of age, however, NOD mice start becoming hyperglycemic, indicating the destruction of the majority of their pancreatic beta cells and the corresponding inability of the pancreas to produce sufficient insulin. Thus, both the cause and the progression of the disease are similar to human IDDM patients.

[0402] *In vivo* assays of efficacy of anti-GMAD antibody therapy can be assessed in female NOD/LtJ mice (commercially available from The Jackson Laboratory, Bar Harbor, Me.). In the literature, it's reported that 80% of female mice develop diabetes by 24 weeks of age and onset of insulinitis begins between 6-8 weeks age. NOD mice are inbred and highly responsive to a variety of immunoregulatory strategies. Adult NOD mice (6-8 weeks of age) have an average mass of 20-25 g.

[0403] These mice can be either untreated (control), treated with the therapeutics of the subject invention (e.g., specific GMAD antibodies and/or fragments and variants thereof), alone or in combination with other therapeutic compounds stated above. The effect of these various treatments on the progression of diabetes can be measured as follows:

[0404] At 14 weeks of age, the female NOD mice can be phenotyped according to glucose tolerance. Glucose tolerance can be measured with the intraperitoneal glucose tolerance test (IPGTT). Briefly, blood is drawn from the paraorbital plexus at 0 minutes and 60 minutes after the intraperitoneal injection of glucose (1 g/kg body weight). Normal tolerance is defined as plasma glucose at 0 minutes of less than 144 mg %, or at 60 minutes of less than 160 mg %. Blood glucose levels are determined with a Glucometer Elite apparatus.

[0405] Based upon this phenotypic analysis, animals can be allocated to the different experimental groups. In particular, animals with more elevated blood glucose levels can be assigned to the impaired glucose tolerance group. The mice can be fed ad libitum and can be supplied with acidified water (pH 2.3).

[0406] The glucose tolerant and intolerant mice can be further subdivided into control, and treatment groups (e.g. with anti-GMAD antibodies of the invention) in the presence or absence of other anti-diabetic drugs. Mice in the control group can receive an

interperitoneal injection of vehicle daily, six times per week. Mice in the treatment group can receive an interperitoneal injection of the specific anti-GMAD antibodies and fragments and variants thereof, in vehicle daily, six times per week.

[0407] The level of urine glucose in the NOD mice can be determined on a bi-weekly basis using Labstix (Bayer Diagnostics, Hampshire, England). Weight and fluid intake can also be determined on a bi-weekly basis. The onset of diabetes is defined after the appearance of glucosuria on two consecutive determinations. After 10 weeks of treatment, an additional IPGTT can be performed and animals can be sacrificed the following day.

[0408] Over the 10 week course of treatment, control animals in both the glucose tolerant and glucose intolerant groups develop diabetes at a rate of 60% and 86%, respectively (see US patent No. 5,866,546, Gross et al.). Thus, high rates of diabetes occur even in NOD mice which are initially glucose tolerant if no intervention is made.

[0409] Results can be confirmed by the measurement of blood glucose levels in NOD mice, before and after treatment. Blood glucose levels are measured as described above in both glucose tolerant and intolerant mice in all groups described.

[0410] Additionally, the therapeutics of the subject invention (e.g., specific GMAD antibodies and fragments and variants thereof) can be quantified using spectrometric analysis and appropriate protein quantities can be resuspended prior to injection in 50 microliter phosphate buffered saline (PBS) per dose. Two injections, one week apart, can be administered subcutaneously under the dorsal skin of each mouse. Monitoring can be performed on two separate occasions prior to immunization and can be performed weekly throughout the treatment and continued thereafter. Urine can be tested for glucose every week (Keto-Diastix.RTM.; Miles Inc., Kankakee, Ill.) and glycosuric mice can be checked for serum glucose (ExacTech.RTM., MediSense, Inc., Waltham, Mass.). Diabetes is diagnosed when fasting glycemia is greater than 2.5g/L.

#### **Example 6: Histological Examination of NOD Mice.**

[0411] Histological examination of tissue samples from NOD mice can demonstrate the ability of the compositions of the present invention, and/or a combination of the compositions of the present invention with other therapeutic agents for diabetes, to increase the relative concentration of beta cells in the pancreas. The experimental method is as follows:



[0412] The mice from Example 6 can be sacrificed at the end of the treatment period and tissue samples can be taken from the pancreas. The samples can be fixed in 10% formalin in 0.9% saline and embedded in wax. Two sets of 5 serial 5 micron sections can be cut for immunolabelling at a cutting interval of 150 microns. Sections can be immunolabelled for insulin (guinea pig anti-insulin antisera dilution 1:1000, ICN Thames U.K.) and glucagon (rabbit anti-pancreatic glucagon antisera dilution 1:2000) and detected with peroxidase conjugated anti-guinea pig (Dako, High Wycombe, U.K.) or peroxidase conjugated anti-rabbit antisera (dilution 1:50, Dako).

[0413] The composition of the present invention may or may not have as strong an effect on the visible mass of beta cells as it does on the clinical manifestations of diabetes in glucose tolerant and glucose intolerant animals.

**Example 7: *In vivo* Mouse Model of NIDDM.**

[0414] Male C57BL/6J mice from Jackson Laboratory (Bar Harbor, ME) can be obtained at 3 weeks of age and fed on conventional chow or diets enriched in either fat (35.5% wt/wt; Bioserv.Frenchtown, NJ) or fructose (60% wt/wt; Harlan Teklad, Madison, WI). The regular chow is composed of 4.5% wt/wt fat, 23% wt/wt protein, 31.9% wt/wt starch, 3.7% wt/wt fructose, and 5.3% wt/wt fiber. The high-fat (lard) diet is composed of 35.5% wt/wt fat, 20% wt/wt protein, 36.4% wt/wt starch, 0.0% wt/wt fructose, and 0.1% wt/wt fiber. The high-fructose diet is composed of 5% wt/wt fat, 20% wt/wt protein, 0.0% wt/wt starch, 60% wt/wt fructose, and 9.4% wt/wt fiber. The mice may be housed no more than five per cage at 22° +/- 3°C temperature- and 50% +/- 20% humidity-controlled room with a 12-hour light (6 am to 6 pm)/dark cycle (Luo et al., Metabolism 47(6): 663-8 (1998), "Nongenetic mouse models of non-insulin-dependent diabetes mellitus"; Larsen et al., Diabetes 50(11): 2530-9 (2001), "Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats"). After exposure to the respective diets for 3 weeks, mice can be injected intraperitoneally with either streptozotocin, "STZ" (Sigma, St. Louis, MO), at 100 mg/kg body weight or vehicle (0.05 mol/L citric acid, pH 4.5) and kept on the same diet for the next 4 weeks. Under nonfasting conditions, blood is obtained 1, 2, and 4 weeks post-STZ by nipping the distal part of the tail. Samples are used to measure nonfasting plasma glucose and insulin concentrations. Body weight and food intake are recorded weekly.

[0415] To directly determine the effect of the high-fat diet on the ability of insulin to stimulate glucose disposal, the experiments can be initiated on three groups of mice, fat-fed, chow-fed injected with vehicle, and fat-fed injected with STZ at the end of the 7-week period described above. Mice can be fasted for 4 hours before the experiments. In the first series of experiments, mice can be anesthetized with methoxyflurane (Pitman-Moor, Mundelein, IL) inhalation. Regular insulin (Sigma) can be injected intravenously ([IV] 0.1 U/kg body weight) through a tail vein, and blood can be collected 3, 6, 9, 12, and 15 minutes after the injection from a different tail vein. Plasma glucose concentrations can be determined on these samples, and the half-life ( $t_{1/2}$ ) of glucose disappearance from plasma can be calculated using WinNonlin (Scientific Consulting, Apex, NC), a pharmacokinetics/pharmacodynamics software program.

[0416] In the second series of experiments, mice can be anesthetized with intraperitoneal sodium pentobarbital (Sigma). The abdominal cavity is opened, and the main abdominal vein is exposed and catheterized with a 24-gauge IV catheter (Johnson-Johnson Medical, Arlington, TX). The catheter is secured to muscle tissue adjacent to the abdominal vein, cut on the bottom of the syringe connection, and hooked to a prefilled PE50 plastic tube, which in turn is connected to a syringe with infusion solution. The abdominal cavity is then sutured closed. With this approach, there would be no blockage of backflow of the blood from the lower part of the body. Mice can be infused continuously with glucose (24.1 mg/kg/min) and insulin (10 mU/kg/min) at an infusion volume of 10  $\mu$ L/min. Retro-orbital blood samples (70  $\mu$ L each) can be taken 90, 105, 120, and 135 minutes after the start of infusion for measurement of plasma glucose and insulin concentrations. The mean of these four samples is used to estimate steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations for each animal.

[0417] Finally, experiments to evaluate the ability of the antibody of the present application, either alone or in combination with any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus, to decrease plasma glucose can be performed in the following two groups of "NIDDM" mice models that are STZ-injected: (1) fat-fed C57BL/6J, and (2) fructose-fed C57BL/6J. Plasma glucose concentrations of the mice for these studies may range from 255 to 555 mg/dL. Mice are randomly assigned to treatment with either vehicle, antibodies of the present invention either alone or in combination with any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus. A total of three doses may be administered. Tail vein blood samples can be taken for

measurement of the plasma glucose concentration before the first dose and 3 hours after the final dose.

[0418] Plasma glucose concentrations can be determined using the Glucose Diagnostic Kit from Sigma (Sigma No. 315), an enzyme colorimetric assay. Plasma insulin levels can be determined using the Rat Insulin RIA Kit from Linco Research (#RI-13K; St. Charles, MO).

[0419] It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples.

[0420] Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[0421] The entire disclosure of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference.

[0422] Further, the Sequence Listing submitted herewith, in both computer and paper forms, is hereby incorporated by reference in its entirety.

[0423] The entire disclosure (including the specification, sequence listing, and drawings) of Provisional Application No. 60/368,813 filed April 1, 2002 is herein incorporated by reference in its entirety.

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 25, Paragraph 62.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit

August 21, 1997

Accession Number

209215

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**ATCC Deposit No. 209215**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209215

## UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

## DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

**What is Claimed Is:**

1. An antibody that specifically binds to a GMAD polypeptide wherein said antibody comprises a first amino acid sequence at least 95% identical to an second amino acid sequence selected from the group consisting of:
  - (a) an amino acid sequence comprising the amino acid sequence of a VHCDR of any one of the scFvs of SEQ ID NOS:1 through 136; and
  - (b) an amino acid sequence comprising the amino acid sequence of a VLCDR of any one of the scFvs of SEQ ID NOS:1 through 136.
2. The antibody of claim 1, wherein the second amino acid sequence consists of the amino acid sequence of a VHCDR3 of any one of the scFvs of SEQ ID NOS:1 through 136.
3. The antibody of claim 1, wherein the second amino acid sequence consists of the amino acid sequence of a VH domain of any one of the scFvs of SEQ ID NOS:1 through 136.
4. The antibody of claim 2, wherein the second amino acid sequence consists of the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 136.
5. The antibody of claim 3, which also comprises an amino acid sequence at least 95% identical to the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 136.
6. The antibody of claim 5, wherein the VH and VL domains are from the same scFv.
7. The antibody of claim 1 wherein the first amino acid sequence is identical to the second amino acid sequence.
8. The antibody of claim 7 wherein the second amino acid sequence consists of the amino acid sequence of a VH domain of any one of the scFvs of SEQ ID NOS:1 through 136.

9. The antibody of claim 7 wherein the second amino acid sequence consists of the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 136.
10. The antibody of claim 8 which also comprises an amino acid sequence 100% identical to the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 136.
11. The antibody of claim 4, wherein the GMAD polypeptide is a GMAD homodimer.
12. The antibody of claim 4, wherein the GMAD polypeptide is purified from a cell culture wherein cells in said cell culture comprise a polynucleotide encoding amino acids 1 to 108 of SEQ ID NO:2 operably associated with a regulatory sequence that controls expression of said polynucleotide.
13. The antibody of claim 4, wherein the antibody is selected from the group consisting of:
- (a) a whole immunoglobulin molecule;
  - (b) an scFv;
  - (c) a monoclonal antibody;
  - (d) a human antibody;
  - (e) a chimeric antibody;
  - (f) a humanized antibody;
  - (g) a Fab fragment;
  - (h) an Fab' fragment;
  - (i) an F(ab')<sub>2</sub>;
  - (j) an Fv; and
  - (k) a disulfide linked Fv.
14. The antibody of claim 4, wherein the antibody has a dissociation constant ( $K_D$ ) less than or equal to  $10^{-7}$  M.
15. The antibody of claim 14, wherein the antibody has a dissociation constant ( $K_D$ ) less than or equal to  $10^{-9}$  M.



16. The antibody of claim 15, wherein the antibody has a dissociation constant ( $K_D$ ) less than or equal to  $10^{-10}$  M.

17. The antibody of claim 16, wherein the antibody has a dissociation constant ( $K_D$ ) less than or equal to  $10^{-11}$  M.

18. The antibody of claim 17, wherein the antibody has a dissociation constant ( $K_D$ ) less than or equal to  $10^{-12}$  M.

19. The antibody of claim 14, wherein the antibody has an off rate less than or equal to  $10^{-3}$ /sec.

20. The antibody of claim 19, wherein the antibody has an off rate less than or equal to  $10^{-4}$ /sec.

21. The antibody of claim 20, wherein the antibody has an off rate less than or equal to  $10^{-5}$ /sec.

22. The antibody of claim 21, wherein the antibody has an off rate less than or equal to  $10^{-6}$ /sec.

23. The antibody of claim 22, wherein the antibody has an off rate less than or equal to  $10^{-7}$ /sec.

24. The antibody of claim 4, wherein the antibody is labeled.

25. The antibody of claim 24, which is labeled with a radioisotope.

26. The antibody of claim 25, wherein the radioisotope is  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$ ,  $^{90}\text{Y}$ ,  $^{99}\text{Tc}$ ,  $^{177}\text{Lu}$ ,  $^{166}\text{Ho}$ , or  $^{153}\text{Sm}$ ,  $^{215}\text{Bi}$ , or  $^{225}\text{Ac}$ .

27. The antibody of claim 24, which is labeled with an enzyme, a fluorescent label, a luminescent label, or a bioluminescent label.

28. The antibody of claim 4, wherein the antibody is biotinylated.

29. The antibody of claim 4, wherein the antibody is conjugated to a therapeutic or cytotoxic agent.

30. The antibody of claim 29, wherein the therapeutic or cytotoxic agent is selected from the group consisting of:

- (a) an anti-metabolite,
- (b) an alkylating agent;
- (c) an antibiotic;
- (d) a growth factor;
- (e) a cytokine;
- (f) an anti-angiogenic agent;
- (g) an anti-mitotic agent;
- (h) an anthracycline;
- (i) toxin; and
- (j) an apoptotic agent.

31. The antibody of claim 4, that inhibits the activity of a GMAD polypeptide or a fragment thereof.

32. The antibody of claim 31, that diminishes or abolishes the ability of a GMAD polypeptide or a fragment thereof to bind to its receptor.

33. The antibody of claim 31, that diminishes or abolishes the ability of a GMAD polypeptide or a fragment thereof to inhibit insulin action.

34. The antibody of claim 4 covalently linked to a heterologous polypeptide.

35. The antibody of claim 4 in a pharmaceutically acceptable carrier.

36. A kit comprising the antibody of claim 4.

37. An isolated nucleic acid molecule encoding the antibody of claim 4.

38. A vector comprising the isolated nucleic acid molecule of claim 37.

39. The vector of claim 38 which also comprises at least one nucleotide sequence which regulates the expression of the antibody encoded by the nucleic acid molecule.

40. A host cell comprising the nucleic acid molecule of claim 39.

41. A cell line engineered to express the antibody of claim 4.
42. An antibody that binds the same epitope as the antibody of claim 10.
43. An antibody that competitively inhibits the binding of the antibody of claim 10 to a GMAD polypeptide.
44. The antibody of claim 43 that competitively inhibits the binding of the antibody of claim 10 to a GMAD polypeptide by at least 50%.
45. The antibody of claim 43 that competitively inhibits the binding of the antibody of claim 10 to a GMAD polypeptide by at least 70%.
46. The antibody of claim 43 that competitively inhibits the binding of the antibody of claim 10 to a GMAD polypeptide by at least 90%.
47. The antibody of claim 43 that competitively inhibits the binding of the antibody of claim 10 to a GMAD polypeptide by at least 95%.
48. A method for detecting aberrant expression of GMAD polypeptide, comprising:
  - (a) assaying the level of GMAD polypeptide expression in a first biological sample of an individual using at least one antibody of claim 4; and
  - (b) comparing the level of GMAD polypeptide assayed in biological sample with a standard level of GMAD polypeptide expression or level of GMAD polypeptide in a second, normal biological sample;
  - (c) wherein an increase or decrease in the assayed level of GMAD polypeptide in the first biological sample compared to the standard level of GMAD polypeptide expression or level of GMAD polypeptide in a second, normal biological sample, is indicative of aberrant expression.

49. A method for diagnosing or monitoring diabetes comprising:
- (a) administering to a subject an effective amount of a labeled antibody of claim 24;
  - (b) waiting for a time interval following the administering for permitting the antibody of claim 24 to preferentially concentrate at sites in the subject where GMAD polypeptide is expressed;
  - (c) determining background level; and
  - (d) detecting the labeled antibody of claim 24 in the subject, such that detection of labeled antibody above the background level indicates that the subject has diabetes.
50. The method of claim 49 wherein said diabetes is type II diabetes.
51. A method of treating, preventing or ameliorating diabetes comprising administering to an animal in need thereof, the antibody of claim 4 in an amount effective to treat, prevent or ameliorate the disease or disorder.
52. The method of claim 51, wherein said diabetes is type II diabetes.
53. The method of claim 51, wherein said antibody is administered in combination with an anti-diabetic agent.

## SEQUENCE LISTING

&lt;110&gt; Human Genomes Sciences, Inc.

&lt;120&gt; Antibodies that Specifically Bind to GMAD

&lt;130&gt; PF584PCT

&lt;140&gt; Not assigned

&lt;141&gt; 2003-03-28

&lt;150&gt; 60/368,813

&lt;151&gt; 2002-04-01

&lt;160&gt; 234

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Lys Ser Ser Ser Phe Ala Asn Ala Phe Asp Ile Trp Gly Gln Gly  
100 105 110

Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
115 120 125

Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser  
130 135 140

Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu  
145 150 155 160

Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro  
165 170 175

Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp  
 180 185 190

Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr  
 195 200 205

Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp  
 210 215 220

Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val  
 225 230 235 240

Leu Gly

<210> 44  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC607

<400> 44

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Met  
 65 70 75 80

Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly

115                      120                      125  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
     130                      135                      140  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
     145                      150                      155                      160  
 Thr Ser Ser Asp Val Gly Asp Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
                     165                      170                      175  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
                     180                      185                      190  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
                     195                      200                      205  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
                     210                      215                      220  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
     225                      230                      235                      240  
 Thr Lys Leu Thr Val Leu Gly  
                     245  
  
 <210> 45  
 <211> 246  
 <212> PRT  
 <213> Artificial sequence  
  
 <220>  
 <223> scFv protein GMBC608  
  
 <400> 45  
 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg  
     1                      5                      10                      15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser  
                     20                      25                      30  
 Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Glu Gly Leu Glu Phe Val  
                     35                      40                      45  
 Ser Tyr Ile Ser Ser Gly Ser Ser Thr Thr Tyr Tyr Thr Asp Ser Val  
                     50                      55                      60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Arg Ser Ile Ser Ser Asp Tyr Tyr Ser Tyr Tyr Leu Asp Val  
 100 105 110

Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
 115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp  
 130 135 140

Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln  
 145 150 155 160

Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro  
 165 170 175

Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser  
 180 185 190

Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser  
 195 200 205

Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys  
 210 215 220

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr  
 225 230 235 240

Lys Leu Thr Val Leu Gly  
 245

<210> 46

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC609

<400> 46

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Glu

1 5 10 15

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Glu Phe Asn Tyr Ala  
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

Gly Arg Ser Arg Ser Glu Ala Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
50 55 60

Pro Leu Gln Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
65 70 75 80

Leu Tyr Leu Gln Val Asn Ser Leu Lys Ile Glu Asp Thr Gly Val Tyr  
85 90 95

Phe Cys Lys Trp Glu Lys Ser Glu Tyr Tyr Gly Met Asp Val Trp Gly  
100 105 110

Arg Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro  
130 135 140

Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile Ser Cys Ser Gly  
145 150 155 160

Ser Thr Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp Tyr Gln Gln His  
165 170 175

Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Lys Arg Pro  
180 185 190

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Ser Ala  
195 200 205

Ser Leu Asp Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr  
210 215 220

Cys Ala Ala Trp Asp Asp Ser Leu Ser Glu Phe Leu Phe Gly Thr Gly  
225 230 235 240

Thr Lys Leu Thr Val Leu Gly

245

<210> 47  
 <211> 241  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC610

<400> 47

Gln Val Thr Leu Lys Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Phe Thr Phe Gly Ala Tyr  
 20 25 30

Tyr Ile His Trp Val Arg Gln Val Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Trp Ile Asp Pro Asn Asn Gly Gly Thr Asn Tyr Ala Gln Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Met Ser Thr Thr Thr Tyr  
 65 70 75 80

Met Glu Val Ser Gly Leu His Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Ala Arg Val Ala Thr Ile Leu Glu Tyr Trp Gly Arg Gly Thr  
 100 105 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser  
 115 120 125

Gly Gly Gly Gly Ser Pro Glu Leu Thr Gln Asp Pro Ala Val Ser Val  
 130 135 140

Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg  
 145 150 155 160

Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val  
 165 170 175

Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg  
 180 185 190

Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly  
 195 200 205

Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser  
 210 215 220

Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 225 230 235 240

Gly

<210> 48  
 <211> 239  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC612

<400> 48

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Tyr  
 20 25 30

Gly Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ala Phe Ile Arg Tyr Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Gly Tyr Arg Ile Val Asp Tyr Trp Gly Gln Gly Thr Leu Val  
 100 105 110

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Pro

130                                      135                                      140  
 Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile  
 145                                      150                                      155                                      160  
 Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys  
                                     165                                      170                                      175  
 Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser Arg  
                                     180                                      185                                      190  
 Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser  
                                     195                                      200                                      205  
 Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asn  
                                     210                                      215                                      220  
 Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg  
 225                                      230                                      235  
  
 <210> 49  
 <211> 245  
 <212> PRT  
 <213> Artificial sequence  
  
 <220>  
 <223> scFv protein GMBC613  
  
 <400> 49  
 Lys Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1                                      5                                      10                                      15  
  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser His  
                                     20                                      25                                      30  
  
 Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
                                     35                                      40                                      45  
  
 Ala Ser Ile Lys Gln Asp Gly Arg Glu Lys His Phe Val Asp Ser Val  
                                     50                                      55                                      60  
  
 Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr  
 65                                      70                                      75                                      80  
  
 Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys  
                                     85                                      90                                      95



Ala Arg Glu Thr Tyr Gly Gly Tyr Tyr Tyr Tyr Phe Met Asp Val Trp  
100 105 110

Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly  
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro  
130 135 140

Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly  
145 150 155 160

Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly  
165 170 175

Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly  
180 185 190

Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu  
195 200 205

Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn  
210 215 220

Ser Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys  
225 230 235 240

Leu Thr Val Leu Gly  
245

&lt;210&gt; 50

&lt;211&gt; 247

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; scFv protein GMBC614

&lt;400&gt; 50

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60  
 Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 Thr Lys Leu Thr Val Leu Gly  
 245

<210> 51  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>

&lt;223&gt; scFv protein GMBC615

&lt;400&gt; 51

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Lys Gly Thr Leu Val Ala Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 52

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC616

<400> 52

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr  
 85 90 95

Tyr Cys Thr Trp Asp His Ser Tyr Tyr Tyr Asp Met Ala Val Trp Gly  
 100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro  
 130 135 140

Phe Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 53  
 <211> 243  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC617

<400> 53

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn  
 20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys  
 50 55 60

Gly Arg Phe Thr Ile Ser Arg His Asn Ser Lys Asn Thr Leu Tyr Leu  
 65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala  
 85 90 95

Arg Gly Leu Trp Phe Gly Glu Leu Leu Tyr Trp Gly Gln Gly Thr Leu  
 100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
 115 120 125

Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly  
 130 135 140

Ser Arg Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Thr Gly Asp  
 145 150 155 160

Val Gly Gly Tyr Asp Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys  
 165 170 175

Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val  
 180 185 190

Pro Asp Arg Phe Ser Ala Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Phe Cys Ser Thr  
 210 215 220

Tyr Ala Pro Pro Gly Ile Ile Met Phe Gly Gly Gly Thr Lys Leu Thr  
 225 230 235 240

Val Leu Gly

<210> 54  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC618

<400> 54

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Asp Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Arg Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80  
 Leu Tyr Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro  
 130 135 140  
 Ser Ala Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly  
 145 150 155 160  
 Ser Ser Ser Asn Ile Gly Ser Asn Thr Val Asn Trp Tyr Gln Arg Leu  
 165 170 175  
 Pro Gly Ala Ala Pro Gln Leu Leu Ile Tyr Asn Asn Asp Gln Arg Pro  
 180 185 190  
 Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Gly  
 195 200 205  
 Ser Leu Val Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr  
 210 215 220  
 Cys Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 Thr Lys Leu Thr Val Leu Gly  
 245

<210> 55  
 <211> 244  
 <212> PRT  
 <213> Artificial sequence  
  
 <220>  
 <223> scFv protein GMBC619  
  
 <400> 55

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Tyr  
 20 25 30  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ala Val Ile Thr Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Asp Gly Gly Gly Trp Tyr His Pro Arg Leu Asp Tyr Trp Gly  
 100 105 110  
 Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140  
 Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160  
 Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
 165 170 175  
 Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
 180 185 190  
 Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205  
 Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
 210 215 220  
 Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240



Thr Val Leu Gly

<210> 56  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC620

<400> 56

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 57  
 <211> 241  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC621

<400> 57

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asp Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys  
 85 90 95

Ala Lys Arg Gly Leu Trp Thr Pro Ile Asp Tyr Trp Gly Lys Gly Thr  
 100 105 110

Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Ser  
 115 120 125

Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val  
 130 135 140

Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg  
 145 150 155 160

Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val  
 165 170 175

Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg  
 180 185 190

Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly  
 195 200 205

Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser  
 210 215 220

Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 225 230 235 240

Gly

<210> 58  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC625

<400> 58

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Arg Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asp Thr  
 65 70 75 80

Met Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
                     85                    90                    95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
                     100                    105                    110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
                     115                    120                    125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
                     130                    135                    140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
                     145                    150                    155                    160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
                     165                    170                    175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
                     180                    185                    190

Pro Ser Gly Val Ser Asn Arg Phe Phe Gly Ser Lys Ser Gly Asn Thr  
                     195                    200                    205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
                     210                    215                    220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
                     225                    230                    235                    240

Thr Lys Leu Thr Val Leu Gly  
                     245

<210> 59

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC626

<400> 59

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Glu  
                     1                    5                    10                    15

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Glu Phe Asn Tyr Ala  
 20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ser Arg Ser Glu Ala Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

Pro Leu Gln Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Val Asn Ser Leu Lys Ile Glu Asp Thr Gly Val Tyr  
 85 90 95

Phe Cys Lys Trp Glu Lys Ser Glu Tyr Tyr Gly Met Asp Val Trp Gly  
 100 105 110

Arg Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Arg Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Lys Ser Thr Gln Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 60  
 <211> 244  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC627

<400> 60

Gly Val Gln Leu Val Gln Ser Gly Gly Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Arg Val Ser Cys Lys Ala Ser Arg Tyr Ile Phe Ser Asn Tyr  
 20 25 30

Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Ser Ile Arg Asn Asp Lys Gly Ser Thr Asn Tyr Ala Gln Gly Phe  
 50 55 60

Gln Asp Arg Leu Thr Met Thr Thr Asp Thr Ser Thr Asn Thr Val Phe  
 65 70 75 80

Met Glu Leu Arg Ser Leu Ser Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Ser Ala Pro Tyr Tyr Tyr Gly Met Gly Ile Trp Gly Lys Gly Thr  
 100 105 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
 115 120 125

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser  
 130 135 140

Gly Ser Ser Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser  
 145 150 155 160

Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly  
 165 170 175

Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Gly Asn Arg Pro Ser Gly  
 180 185 190

Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu  
 195 200 205

Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser  
 210 215 220

Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240

Thr Val Leu Gly

<210> 61  
 <211> 249  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC628

<400> 61

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr  
 20 25 30

Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met  
 35 40 45

Gly Trp Ile Ser Ala Tyr Lys Gly Asn Ala Asn Tyr Ala Glu Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Asn Thr Ala Tyr  
 65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Thr Arg Ile Ser Val Ala Gly Leu Asp Tyr Tyr Tyr Tyr Gly  
 100 105 110

Leu Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu  
 130 135 140

Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile  
 145 150 155 160

Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Thr Asn Trp Phe Gln  
 165 170 175

Gln Lys Pro Gly Gln Ala Pro Leu Leu Val Val Tyr Ala Lys Asn Asn  
 180 185 190

Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn  
 195 200 205

Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp  
 210 215 220

Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Val Val Phe Gly  
 225 230 235 240

Gly Gly Thr Lys Leu Thr Val Leu Gly  
 245

<210> 62  
 <211> 244  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC629

<400> 62

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Lys Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Glu Tyr Ala Val  
 50 55 60

Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asp Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95



Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140  
 Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160  
 Ser Leu Arg Ser Tyr Tyr Thr Asn Trp Phe Gln Gln Lys Pro Gly Gln  
 165 170 175  
 Ala Pro Leu Leu Val Val Tyr Ala Lys Asn Lys Arg Pro Ser Gly Ile  
 180 185 190  
 Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205  
 Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys His Ser  
 210 215 220  
 Arg Asp Ser Ser Gly Asn His Val Leu Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240  
 Thr Val Leu Gly

<210> 63  
 <211> 242  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC630

<400> 63

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg  
 1 5 10 15

Ser Leu Arg Leu Pro Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Lys Ala Thr Ser Leu Leu Asn Ala Phe Asp Ile Trp Gly Arg Gly  
 100 105 110

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 115 120 125

Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser  
 130 135 140

Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu  
 145 150 155 160

Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro  
 165 170 175

Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp  
 180 185 190

Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr  
 195 200 205

Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp  
 210 215 220

Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val  
 225 230 235 240

Leu Gly

<210> 64

<211> 244

<212> PRT

<213> Artificial sequence

&lt;220&gt;

&lt;223&gt; scFv protein GMBC632

&lt;400&gt; 64

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Lys Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Glu Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asp Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Asp Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140

Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160

Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
 165 170 175

Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
 180 185 190

Pro Asp Arg Phe Phe Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205

Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
 210 215 220

Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240

Thr Val Leu Gly

<210> 65

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC634

<400> 65

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 66

<211> 244

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC635

<400> 66

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Tyr Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Lys Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140

Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160

Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
 165 170 175

Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
 180 185 190

Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205

Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
 210 215 220

Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240

Thr Val Leu Gly

<210> 67  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC638

<400> 67

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Glu  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Glu Phe Asn Tyr Ala  
 20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ser Arg Ser Val Ala Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

Pro Leu Gln Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Val Asn Ser Leu Lys Ile Glu Asp Thr Gly Val Tyr  
 85 90 95

Phe Cys Lys Trp Glu Lys Ser Glu Tyr Tyr Gly Met Asp Val Trp Gly  
 100 105 110

Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 68

<211> 253

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC639

&lt;400&gt; 68

Gly Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Thr Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn His  
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Ile Glu Trp Val  
 35 40 45

Gly Val Ile Asn Pro Ser Gly Asp Gly Ser Ser Tyr Ala Gln Thr Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
 65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Asp Leu Phe Tyr Asp Phe Trp Ser Asp Tyr Tyr Arg Asn Asp  
 100 105 110

Gln Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Leu Val Thr Val  
 115 120 125

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 130 135 140

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln  
 145 150 155 160

Ala Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala  
 165 170 175

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr  
 180 185 190

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser  
 195 200 205

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu  
 210 215 220

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His  
 225 230 235 240





Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro  
 180 185 190

Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile  
 195 200 205

Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg  
 210 215 220

Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr  
 225 230 235 240

Val Leu Gly

<210> 70  
 <211> 243  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC642

<400> 70

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ile His  
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Ile Ile Asn Pro Gly Asp Gly Ser Thr Ser Tyr Ala Gln Asn Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Ala Gly Arg Thr Val Thr Ser His Phe Asp Tyr Trp Gly Arg  
 100 105 110

Gly Thr Leu Ala Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 115 120 125

Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val  
 130 135 140

Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser  
 145 150 155 160

Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala  
 165 170 175

Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro  
 180 185 190

Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile  
 195 200 205

Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg  
 210 215 220

Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr  
 225 230 235 240

Val Leu Gly

<210> 71  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC645

<400> 71

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Lys Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Glu Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asp Thr  
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
225 230 235 240

Thr Glu Leu Thr Val Leu Gly  
245

<210> 72

<211> 241

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC646

<400> 72

Gly Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr  
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Thr Thr Ser Tyr Ala Gln Lys Phe  
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys  
85 90 95

Ala Arg Glu Arg Phe Leu Arg Gly Met Asp Val Trp Gly Arg Gly Thr  
100 105 110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
115 120 125

Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu  
130 135 140

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln  
145 150 155 160

Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala  
165 170 175

Pro Lys Val Leu Ile Tyr Lys Ala Ser Thr Leu Glu Ser Gly Val Pro  
180 185 190

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile  
195 200 205

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser  
210 215 220

Tyr Ser Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
225 230 235 240

Arg

<210> 73  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC647

<400> 73

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 74

<211> 244

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC648

<400> 74

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Arg Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Thr  
 130 135 140

Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160

Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
 165 170 175

Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
 180 185 190

Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205

Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
 210 215 220

Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240

Thr Val Leu Gly

<210> 75  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC649

<400> 75

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80



Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
                             85                            90                            95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
                             100                            105                            110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
                             115                            120                            125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
                             130                            135                            140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
                             145                            150                            155                            160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
                             165                            170                            175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
                             180                            185                            190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
                             195                            200                            205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
                             210                            215                            220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
                             225                            230                            235                            240

Thr Lys Leu Thr Val Leu Gly  
                             245

<210> 76

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC651

<400> 76

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
                             1                            5                            10                            15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
                             20                            25                            30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 77  
 <211> 247

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; scFv protein GMBC652

&lt;400&gt; 77

Gly Val Gln Leu Val Gln Ser Gly Gly Val Val Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr  
 85 90 95

Tyr Cys Thr Trp Asp His Ser Tyr Tyr Tyr Asp Met Ala Val Trp Gly  
 100 105 110

Arg Gly Thr Met Val Thr Ala Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Phe Met Ile Tyr Asp Val Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Ser Ala Ser Thr Val Ile Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 78  
 <211> 246  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC653

<400> 78

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr  
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr  
 65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Gly Gly Ser Arg Tyr Tyr Gly Met Asp Val Trp Ser Arg Gly  
 100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 115 120 125

Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu Thr Gln Pro Pro Ser Val  
 130 135 140

Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Gly Arg  
 145 150 155 160

Ser Asn Ile Gly Ser Asn Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly  
 165 170 175

Ala Ala Pro Lys Leu Leu Ile Tyr Gly Asn Asp Gln Arg Pro Ser Gly  
 180 185 190

Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu  
 195 200 205

Ala Ile Thr Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln  
 210 215 220

Ser Tyr Asp Ser Ser Leu Arg Gly Ser Arg Val Phe Gly Thr Gly Thr  
 225 230 235 240

Lys Val Thr Val Leu Gly  
 245

<210> 79  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC654

<400> 79

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Glu Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Arg Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Ile Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
                   100                                  105                                  110  
  
 Lys Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
           115                                  120                                  125  
  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
           130                                  135                                  140  
  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145                                  150                                  155                                  160  
  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
                   165                                  170                                  175  
  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
                   180                                  185                                  190  
  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
           195                                  200                                  205  
  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
           210                                  215                                  220  
  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225                                  230                                  235                                  240  
  
 Thr Lys Leu Thr Val Leu Gly  
                   245

<210> 80  
 <211> 239  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC655

<400> 80

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1                  5                                  10                                  15  
  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
           20                                  25                                  30  
  
 Gly Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Gln Glu Trp Val  
           35                                  40                                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Lys Ala Tyr Ser Ser Glu Asp Tyr Trp Gly Arg Gly Thr Met Val  
 100 105 110

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Asn Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala  
 130 135 140

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile  
 145 150 155 160

Asn Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Lys  
 165 170 175

Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg  
 180 185 190

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser  
 195 200 205

Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asn  
 210 215 220

Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg  
 225 230 235

<210> 81

<211> 244

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC657

<400> 81

Gln Met Gln Leu Met Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1                      5                      10                      15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Lys Phe Ser Asp Ala  
                     20                      25                      30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
                     35                      40                      45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Glu Tyr Ala Ala  
                     50                      55                      60

Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asp Thr  
 65                      70                      75                      80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
                     85                      90                      95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
                     100                      105                      110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
                     115                      120                      125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
                     130                      135                      140

Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145                      150                      155                      160

Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
                     165                      170                      175

Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
                     180                      185                      190

Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
                     195                      200                      205

Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
                     210                      215                      220

Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
 225                      230                      235                      240



Thr Val Leu Gly

<210> 82  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC658

<400> 82

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Arg Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 83

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC659

<400> 83

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Glu  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Glu Phe Asn Tyr Ala  
 20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ser Arg Ser Glu Ala Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

Pro Leu Gln Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Val Asn Ser Leu Lys Ile Glu Asp Thr Gly Val Tyr  
 85 90 95

Phe Cys Lys Trp Glu Lys Ser Glu Tyr Tyr Gly Met Asp Val Trp Gly  
 100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 84

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC660

<400> 84

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
                             85                            90                            95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
                             100                            105                            110

Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
                             115                            120                            125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
                             130                            135                            140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
                             145                            150                            155                            160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
                             165                            170                            175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
                             180                            185                            190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
                             195                            200                            205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
                             210                            215                            220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
                             225                            230                            235                            240

Thr Lys Leu Thr Val Leu Gly  
                             245

<210> 85

<211> 243

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC662

<400> 85

Gly Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
                             1                            5                            10                            15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr  
                   20                                  25                                  30

Thr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
                   35                                  40                                  45

Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe  
                   50                                  55                                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr  
                   65                                  70                                  75                                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
                                   85                                  90                                  95

Ala Arg Glu Lys Leu Arg Asp Phe Gln His Trp Gly Gln Gly Thr Leu  
                   100                                  105                                  110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
                   115                                  120                                  125

Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser Gly  
                   130                                  135                                  140

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp  
                   145                                  150                                  155                                  160

Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys  
                                   165                                  170                                  175

Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser Gly Ile  
                                   180                                  185                                  190

Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr  
                   195                                  200                                  205

Ile Ser Arg Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser  
                   210                                  215                                  220

Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Thr  
                   225                                  230                                  235                                  240

Val Leu Gly

<210> 86  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC664

<400> 86

Glu Val Gln Leu Val Glu Thr Gly Gly Ala Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Ser  
 100 105 110

Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 87

<211> 244

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC665

<400> 87

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140

Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
145 150 155 160

Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
165 170 175

Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
180 185 190

Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
195 200 205

Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
210 215 220

Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
225 230 235 240

Thr Val Leu Gly

<210> 88  
<211> 247  
<212> PRT  
<213> Artificial sequence

<220>  
<223> scFv protein GMBC666

<400> 88

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ala Lys Pro Gly Glu  
1 5 10 15

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Glu Phe Asn Tyr Ala  
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

Gly Arg Ser Arg Ser Glu Ala Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
50 55 60

Pro Leu Gln Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
65 70 75 80

Leu Tyr Leu Gln Val Asn Ser Leu Lys Ile Glu Asp Thr Gly Val Tyr  
85 90 95



Phe Cys Lys Trp Glu Lys Ser Glu Tyr Tyr Gly Met Asp Val Trp Gly  
 100 105 110

Lys Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro  
 130 135 140

Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile Ser Cys Ser Gly  
 145 150 155 160

Ser Thr Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp Tyr Gln Gln His  
 165 170 175

Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Lys Arg Pro  
 180 185 190

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Ser Ala  
 195 200 205

Ser Leu Asp Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr  
 210 215 220

Cys Ala Ala Trp Asp Asp Ser Leu Ser Glu Phe Leu Phe Gly Thr Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 89

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC667

<400> 89

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Pro Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Arg Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Asn Ile Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 90

<211> 244

<212> PRT

<213> Artificial sequence

&lt;220&gt;

&lt;223&gt; scFv protein GMBC668

&lt;400&gt; 90

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr  
 85 90 95

Tyr Cys Thr Trp Asp His Ser Tyr Tyr Tyr Asp Met Ala Val Trp Gly  
 100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140

Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160

Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
 165 170 175

Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
 180 185 190

Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205

Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
 210 215 220

Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240

Thr Val Leu Gly

<210> 91  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC669

<400> 91

Gln Val Gln Leu Val Glu Ser Gly Gly Ala Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro  
 130 135 140

Ser Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
                   165                  170                  175

His Pro Gly Lys Ala Pro Lys Phe Met Ile Tyr Asp Val Ser Lys Arg  
                   180                  185                  190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
                   195                  200                  205

Ala Ser Leu Thr Ile Ser Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr  
                   210                  215                  220

Tyr Cys Ser Ser Tyr Thr Ser Ala Ser Thr Val Ile Phe Gly Gly Gly  
                   225                  230                  235                  240

Thr Lys Leu Thr Val Leu Gly  
                   245

<210> 92

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC670

<400> 92

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Lys Pro Gly Gly  
   1                  5                  10                  15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Ala  
                   20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
                   35                  40                  45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
                   50                  55                  60

Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asn Thr  
                   65                  70                  75                  80

Leu Tyr Leu Gln Val Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
                   85                  90                  95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
                   100                  105                  110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 93  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC672

<400> 93

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Glu Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 94

<211> 243

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC673

&lt;400&gt; 94

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Pro Ile Gly Ser His  
 20 25 30

Trp Met Ser Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ala Ser Ile Lys Gln Asp Gly Arg Glu Lys His Phe Val Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Gly Ile Ser Arg Asp Asn Ala Lys Asp Ser Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ile Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Glu Thr Tyr Gly Gly Tyr Tyr Tyr Tyr Phe Met Asp Val Trp  
 100 105 110

Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly  
 115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro  
 130 135 140

Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly  
 145 150 155 160

Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly  
 165 170 175

Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly  
 180 185 190

Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu  
 195 200 205

Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln  
 210 215 220

Thr Trp Gly Pro Gly Ile Arg Val Phe Gly Gly Gly Thr Lys Leu Thr  
 225 230 235 240



Val Leu Gly

<210> 95  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC676

<400> 95

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Ala Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu His Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Pro Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 96

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC678

<400> 96

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro  
 130 135 140

Ser Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Phe Met Ile Tyr Asp Val Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Ser Ala Ser Thr Val Ile Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 97

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC679

<400> 97

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asn Thr  
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr  
85 90 95

Tyr Cys Thr Trp Asp His Ser Tyr Tyr Tyr Asp Met Ala Val Trp Gly  
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
165 170 175

His Pro Gly Lys Ala Pro Lys Leu Val Ile Tyr Glu Gly Ser Lys Arg  
180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
245

<210> 98

<211> 240

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC681

<400> 98

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Lys Gly Gly Thr Gly Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu  
 100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly  
 115 120 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser  
 130 135 140

Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly  
 145 150 155 160

Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro  
 165 170 175

Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser  
 180 185 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser  
 195 200 205

Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser  
 210 215 220

Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg  
 225 230 235 240

<210> 99

<211> 244

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt; .

&lt;223&gt; scFv protein GMBC682

&lt;400&gt; 99

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140

Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160

Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
 165 170 175

Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
 180 185 190

Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205

Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
 210 215 220

Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240

Thr Val Leu Gly

<210> 100  
 <211> 241  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC683

<400> 100

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Lys Arg Ala Ala Ala Gly Thr Leu Asp Tyr Trp Gly Gln Gly Thr  
 100 105 110

Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser  
 115 120 125

Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val  
 130 135 140

Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg  
 145 150 155 160

Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val  
                   165                  170                  175

Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg  
                   180                  185                  190

Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly  
                   195                  200                  205

Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser  
                   210                  215                  220

Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 225                  230                  235                  240

Gly

<210> 101

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC684

<400> 101

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
   1                  5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Asp Ala  
                   20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
                   35                  40                  45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
                   50                  55                  60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
   65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
                   85                  90                  95



Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 102

<211> 244

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC685

<400> 102

Gln Val Gln Leu Val Glu Ser Gly Gly Val Val Val Gln Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Lys Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140

Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160

Ser Leu Arg Ser Tyr Tyr Thr Asn Trp Phe Gln Gln Lys Pro Gly Gln  
 165 170 175

Ala Pro Leu Leu Val Val Tyr Ala Lys Asn Lys Arg Pro Ser Gly Ile  
 180 185 190

Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205

Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys His Ser  
 210 215 220

Arg Asp Ser Ser Gly Asn His Val Leu Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240

Thr Val Leu Gly

<210> 103

<211> 247

<212> PRT

<213> Artificial sequence

<220>

&lt;223&gt; scFv protein GMBC686

&lt;400&gt; 103

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 104

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC687

<400> 104

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Pro Gly Asp Thr Phe Ser Asn Tyr  
 20 25 30

Ile Phe Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Gly Ile Ile Pro Lys Phe Gly Thr Val Asn Asp Ala His Lys Phe  
 50 55 60

Gln Asp Arg Val Thr Ile Ala Ala Asp Glu Ser Thr Asn Thr Ala Ser  
 65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Cys Glu Pro Ile Pro Lys Asp Tyr Gly Asp Val Asn Gly Leu Glu  
 100 105 110

Ile Trp Gly Lys Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly  
 115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr  
 130 135 140

Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile  
 145 150 155 160

Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln  
 165 170 175

Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser  
 180 185 190

Leu Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr  
 195 200 205

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr  
 210 215 220

Tyr Tyr Cys Gln Gln Tyr Ser Asn Tyr Pro Leu Thr Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Glu Ile Lys Arg  
 245

<210> 105

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC689

<400> 105

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro  
 130 135 140

Ser Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Phe Met Ile Tyr Asp Val Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Ser Ala Ser Thr Val Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 106

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC690

<400> 106

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 Thr Ser Ser Asp Val Gly Gly Tyr Ile Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 His Pro Gly Arg Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 Thr Lys Leu Thr Val Leu Gly  
 245

&lt;210&gt; 107

&lt;211&gt; 253

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; scFv protein GMBC691

&lt;400&gt; 107

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15  
 Ser Met Lys Val Ser Cys Lys Thr Ser Gly Asp Thr Phe Asn Gly Phe  
 20 25 30  
 Tyr Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45  
 Gly Arg Ile Asn Pro Asn Gly Gly Gly Thr Asn Tyr Ala Gln Lys Phe  
 50 55 60  
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Met Asn Thr Ala Tyr  
 65 70 75 80  
 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Asp Leu Phe Tyr Asp Phe Trp Ser Asp Tyr Tyr Arg Asn Asp  
 100 105 110  
 Gln Tyr Tyr Tyr Met Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val  
 115 120 125  
 Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 130 135 140  
 Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln  
 145 150 155 160  
 Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala  
 165 170 175  
 Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr  
 180 185 190  
 Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser  
 195 200 205  
 Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu  
 210 215 220  
 Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His  
 225 230 235 240



Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly  
                   245                                   250

<210> 108  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC692

<400> 108

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1                                   5                                   10                                   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
                   20                                   25                                   30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
                   35                                   40                                   45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
                   50                                   55                                   60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65                                   70                                   75                                   80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
                   85                                   90                                   95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
                   100                                   105                                   110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
                   115                                   120                                   125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
                   130                                   135                                   140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145                                   150                                   155                                   160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
                   165                                   170                                   175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
                   180                                   185                                   190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 109

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC693

<400> 109

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Lys Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asp Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 110  
 <211> 241  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC696

<400> 110

Glu Val Gln Leu Val Gln Ser Arg Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Tyr Thr Phe Asn Gly Tyr  
 20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Trp Ile Asp Pro Ile Asn Ser Val Thr Asn Tyr Ala Gln Asn Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr  
 65 70 75 80

Met Glu Leu Ser Arg Leu Thr Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
                     85                    90                    95

Ala Arg Ala Arg Val Ser Thr Ile Leu Gln Tyr Trp Gly Gln Gly Thr  
                     100                    105                    110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
                     115                    120                    125

Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val  
                     130                    135                    140

Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg  
                     145                    150                    155                    160

Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val  
                     165                    170                    175

Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg  
                     180                    185                    190

Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly  
                     195                    200                    205

Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser  
                     210                    215                    220

Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
                     225                    230                    235                    240

Gly

<210> 111  
 <211> 242  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC725

<400> 111

Glu Val Gln Leu Val Gln Thr Gly Gly Gly Val Val Gln Pro Gly Gly  
 1                    5                    10                    15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ala Phe Ile Leu Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Lys Ser Ser Ser Ser Ala Ser Ala Phe Asp Ile Trp Arg Gln Arg  
 100 105 110

Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 115 120 125

Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser  
 130 135 140

Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu  
 145 150 155 160

Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro  
 165 170 175

Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp  
 180 185 190

Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr  
 195 200 205

Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp  
 210 215 220

Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val  
 225 230 235 240

Leu Gly

<210> 112  
 <211> 247  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMBC727

<400> 112

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Thr Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Met Lys Ser Lys Gly Ser Gly Gly Thr Arg Asp Tyr Ala Ala  
 50 55 60

Pro Val Asn Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Asn Thr Glu Asp Thr Gly Val Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 113

<211> 244

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC729

<400> 113

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Lys Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Glu Tyr Ala Ala  
 50 55 60

Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asp Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asp Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140

Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160

Ser Leu Arg Asn Tyr Tyr Thr Asn Trp Phe Gln Gln Lys Pro Gly Gln  
 165 170 175

Ala Pro Leu Leu Val Val Tyr Ala Lys Asn Lys Arg Pro Ser Gly Ile  
 180 185 190

Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205

Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys His Ser  
 210 215 220

Arg Asp Ser Ser Gly Asn His Val Leu Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240

Thr Val Leu Gly

<210> 114

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMBC730

<400> 114

Gln Val Gln Leu Val Glu Ser Gly Gly Asp Ser Val Lys Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Gly Arg Met Lys Ser Lys Gly Ser Gly Gly Thr Arg Asp Tyr Ala Ala  
 50 55 60

Pro Val Asn Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Asn Thr Glu Asp Thr Gly Val Tyr  
 85 90 95



Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asp Val Trp Gly  
 100 105 110

Lys Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

Thr Lys Leu Thr Val Leu Gly  
 245

<210> 115

<211> 245

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMCC101

<400> 115

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Arg Thr Tyr  
 20 25 30

Ala Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45

Gly Gly Ile Ile Pro Ile Ser Ala Thr Ala Asn Tyr Ala Gln Lys Phe  
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Met Ser Thr Ala Tyr  
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Asp Arg Glu Pro His Tyr Phe Asp Asn Trp Gly Arg Gly Thr  
100 105 110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser  
115 120 125

Gly Gly Gly Gly Ser Ala Leu Pro Val Leu Thr Gln Pro Pro Ser Val  
130 135 140

Ser Glu Ala Pro Arg Gln Gly Val Thr Ile Ser Cys Ser Gly Ser Ser  
145 150 155 160

Ser Asn Ile Gly Asn Asn Ala Val Ser Trp Tyr Gln Gln Leu Pro Gly  
165 170 175

Gln Ala Pro Lys Leu Leu Ile Tyr Tyr Asp Asp Leu Leu Pro Ser Gly  
180 185 190

Val Ser Asp Arg Phe Ser Ala Ser Lys Ser Gly Thr Ser Ala Ser Leu  
195 200 205

Ala Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala  
210 215 220

Ala Trp Asp Asp Ser Leu Asn Gly Val Ile Phe Gly Gly Gly Thr Gln  
225 230 235 240

Leu Thr Val Leu Ser  
245

<210> 116  
<211> 260  
<212> PRT  
<213> Artificial sequence

&lt;220&gt;

&lt;223&gt; scFv protein GMCC102

&lt;400&gt; 116

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Pro Gly Tyr Thr Phe Thr Ser Tyr  
 20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Gly Gly Ala Arg Ser Asn Asp Ser Ser Gly Tyr Tyr Lys Ser  
 100 105 110

Pro Leu Ser Tyr Tyr Tyr Gly Met Asp Val Trp Gly Arg Gly Thr Met  
 115 120 125

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
 130 135 140

Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser  
 145 150 155 160

Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser  
 165 170 175

Asn Ile Gly Ser Asn Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr  
 180 185 190

Ala Pro Lys Leu Leu Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val  
 195 200 205

Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala  
 210 215 220

Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala  
 225 230 235 240

Trp Asp Asp Ser Leu Asn Gly Val Val Phe Gly Gly Gly Thr Lys Val  
 245 250 255

Thr Val Leu Gly  
 260

<210> 117  
 <211> 250  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMCC105

<400> 117

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Asn Leu Gly Ser His  
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ala Val Ile Gly Phe Asp Gly Thr Thr Lys Tyr Tyr Val Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Ser  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Val Arg Glu Asp Tyr Tyr Tyr Asp Ser Ser Gly Tyr Tyr Phe Asp Tyr  
 100 105 110

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
 115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu  
 130 135 140

Thr Gln Asp Pro Phe Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile  
145 150 155 160

Ala Cys Arg Gly Asp Ser Leu Arg Asp Ser Tyr Ala Ser Trp Tyr Gln  
165 170 175

Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Val Tyr Gly Asn Asn Leu  
180 185 190

Arg Pro Ser Gly Ile Pro Gly Arg Phe Ser Gly Ser Ser Ser Gly Asp  
195 200 205

Thr Ala Ser Leu Ser Ile Thr Glu Thr Gln Ala Gly Asp Glu Ala Asp  
210 215 220

Tyr Tyr Cys Ser Ser Arg Gly Asn Ser Thr Ser Arg Leu Tyr Val Phe  
225 230 235 240

Gly Thr Gly Thr Lys Leu Thr Val Leu Gly  
245 250

<210> 118

<211> 245

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMCC106

<400> 118

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly  
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Val Gly Ser Ile Asn Glu Ser  
20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp  
35 40 45

Ile Gly Glu Ile Tyr Pro Thr Gly Thr Thr Asn Tyr Asn Pro Ser Leu  
50 55 60

Glu Ser Arg Val Thr Ile Ser Val Asp Lys Ser Arg Asn Leu Phe Ser  
65 70 75 80

Leu Lys Leu Lys Ser Val Thr Ala Ala Asp Ser Ala Met Tyr Phe Cys  
85 90 95

Ala Arg Asp Arg Trp Ala Gly Gly Phe Asp Leu Trp Gly Arg Gly Thr  
                   100                  105                  110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
           115                  120                  125

Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Ala  
       130                  135                  140

Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser  
   145                  150                  155                  160

Ser Asn Ile Gly Ser Asn Ser Val Tyr Trp Tyr Gln Gln Leu Pro Gly  
                   165                  170                  175

Thr Ala Pro Lys Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly  
           180                  185                  190

Val Pro Asp Arg Phe Ser Ala Ser Lys Ser Gly Thr Ser Ala Ser Leu  
           195                  200                  205

Ala Ile Ser Gly Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala  
       210                  215                  220

Ala Trp Asp Asp Ser Leu Ser Gly Leu Val Phe Gly Gly Gly Thr Lys  
   225                  230                  235                  240

Leu Thr Val Leu Gly  
                   245

<210> 119

<211> 250

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMCC107

<400> 119

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
   1                  5                  10                  15

Ser Val Lys Val Ser Cys Arg Thr Ser Gly Tyr Thr Phe Thr Asp His  
           20                  25                  30

Ser Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Phe Glu Trp Met  
           35                          40                          45

Gly Trp Ile Gly Ala Asp Ser Gly Ser Thr Gln Tyr Ser Arg Asn Phe  
           50                          55                          60

Gln Gly Arg Leu Thr Ile Gly Arg Asp Thr Ser Ala Ser Thr Val Tyr  
           65                          70                          75                          80

Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
                           85                          90                          95

Ala Arg Val Gly Gly Gly Gln Gly Trp Tyr Ser Gly Met Asp Val Trp  
                           100                          105                          110

Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly  
           115                          120                          125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr Gln  
           130                          135                          140

Pro Ser Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys  
           145                          150                          155                          160

Thr Gly Ser Ser Ser Asn Ile Gly Ala Ser Tyr Asp Val His Trp Tyr  
                           165                          170                          175

Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Asn Asn Asn  
                           180                          185                          190

Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Arg Ser Gly  
           195                          200                          205

Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala  
           210                          215                          220

Asp Tyr Tyr Cys His Ser Tyr Asp Ser Asn Leu Ser Gly Asp Val Phe  
           225                          230                          235                          240

Gly Ser Gly Thr Lys Leu Thr Val Leu Gly  
                           245                          250

<210> 120  
 <211> 255  
 <212> PRT  
 <213> Artificial sequence

&lt;220&gt;

&lt;223&gt; scFv protein GMCC108

&lt;400&gt; 120

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Glu Pro Gly Ala  
 1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile Ser Tyr  
 20 25 30

His Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Asp Thr Thr Tyr Ala Gln Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
 65 70 75 80

Met Glu Leu Arg Ser Leu Arg Phe Glu Asp Thr Ala Arg Tyr Tyr Cys  
 85 90 95

Ala Arg Asp Leu Lys Phe Tyr Asp Phe Arg Ser Gly Lys Tyr Gln Asp  
 100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala  
 130 135 140

Gln Ser Val Leu Thr Gln Pro Pro Ser Leu Ser Val Ala Pro Gly Gln  
 145 150 155 160

Thr Ala Ser Ile Thr Cys Gly Gly Asn Asp Ile Gly Thr Lys Ser Val  
 165 170 175

His Trp Tyr Gln Leu Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr  
 180 185 190

Asp Asn Arg Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
 195 200 205

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Gly Gly  
 210 215 220



Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ile Asp His  
 225 230 235 240

Ser Glu Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu Gly  
 245 250 255

<210> 121  
 <211> 244  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMCC109

<400> 121

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Lys Ser Gln Trp Ser Gly Ser Tyr Tyr Gly Ser Phe Asp Tyr Trp  
 100 105 110

Gly Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly  
 115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln  
 130 135 140

Pro Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Thr Ile Thr Cys  
 145 150 155 160

Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val Ser Trp Tyr Gln Lys Lys  
                   165                  170                  175

Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gln Asp Asp Lys Arg Pro  
                   180                  185                  190

Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala  
                   195                  200                  205

Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Gly Asp Tyr Tyr  
                   210                  215                  220

Cys Gln Ala Trp Asp Arg Ser Val Ile Phe Gly Gly Gly Thr Lys Val  
                   225                  230                  235                  240

Thr Val Leu Gly

<210> 122  
 <211> 250  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMCC110

<400> 122

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln  
   1                  5                  10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ala Ser Ile Ser Ser Gly  
                   20                  25                  30

Gly Tyr Arg Trp Ile Trp Ile Arg Gln His Pro Gly Gln Gly Leu Glu  
                   35                  40                  45

Trp Ile Gly Asp Ile His Tyr Ser Gly Ser Thr Gln Tyr Asn Pro Ser  
                   50                  55                  60

Leu Lys Ser Arg Val Ala Leu Thr Leu Asp Arg Ser Lys Asn Gln Phe  
   65                  70                  75                  80

Ser Leu Gln Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr  
                   85                  90                  95

Cys Ala Arg Asp Pro Arg Gly His Thr Tyr Gly Tyr Gly Tyr Tyr Phe  
                   100                  105                  110

Asp Tyr Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly  
 115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser  
 130 135 140

Glu Leu Thr Gln Asp Pro Asp Val Ser Val Ala Leu Gly Gln Thr Val  
 145 150 155 160

Thr Ile Thr Cys Gln Gly Asp Arg Leu Arg Arg Tyr Tyr Ala Ser Trp  
 165 170 175

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Phe Arg Lys  
 180 185 190

Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser  
 195 200 205

Gly Asp Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu  
 210 215 220

Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Thr Ser Gly Thr Leu Ser Phe  
 225 230 235 240

Gly Gly Gly Thr Gln Leu Thr Val Leu Ser  
 245 250

<210> 123

<211> 245

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMCC112

<400> 123

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Thr Tyr  
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ser Gly Val Ser Asp Gly Gly Asp Thr Phe Tyr Ala Asp Ser Val Arg  
 50 55 60

Gly Arg Phe Thr Leu Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe Leu  
 65 70 75 80

Gln Met Asn Ser Leu Thr Ala Glu Asp Thr Ala Thr Tyr Tyr Cys Ala  
 85 90 95

Lys Glu Ile Ala Arg Ile Gly Val Pro Asn Phe Asp His Trp Gly Gln  
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 115 120 125

Gly Ser Gly Gly Gly Gly Ser Ala Leu Glu Thr Thr Leu Thr Gln Ser  
 130 135 140

Pro Gly Thr Leu Ser Leu Ser Pro Gly Asp Arg Ala Thr Leu Ser Cys  
 145 150 155 160

Arg Ala Ser Gln Ser Ile Arg Asn Asn Asp Val Ala Trp Tyr Gln Gln  
 165 170 175

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Ala Ser Arg Arg  
 180 185 190

Ala Thr Asp Ile Pro Asp Arg Phe Ser Gly Ser Ala Ser Gly Thr Asp  
 195 200 205

Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Met Tyr  
 210 215 220

Tyr Cys Gln Gln Tyr Gly Gly Ser Ala Ser Phe Gly Gln Gly Thr Arg  
 225 230 235 240

Leu Glu Ile Lys Arg  
 245

<210> 124

<211> 250

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMCC114

&lt;400&gt; 124

Glu Val Gln Leu Val Glu Ser Gly Pro Glu Val Lys Lys Pro Gly Ser  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ala Ala Ala Phe Ser Ser  
 20 25 30

Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Glu Trp  
 35 40 45

Met Gly Gly Ile Ile Pro Ile Ser Asp Thr Pro Lys Tyr Ala His Lys  
 50 55 60

Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Thr Thr Val  
 65 70 75 80

Phe Met Glu Val Ser Gly Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr  
 85 90 95

Cys Ala Thr Thr Thr Arg Tyr Gly Ser Gly Thr Tyr Asp Tyr Met Asp  
 100 105 110

Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly  
 115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu  
 130 135 140

Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg  
 145 150 155 160

Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr  
 165 170 175

Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Phe Tyr Gly Lys Asn  
 180 185 190

Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Thr Ser Gly  
 195 200 205

Asn Thr Ala Ser Leu Ser Ile Thr Gly Ala Leu Ala Asp Asp Glu Ala  
 210 215 220

Asp Tyr Tyr Cys His Ser Arg Asp Thr Ser Gly Ala Gln Ile Leu Phe  
 225 230 235 240

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly  
245 250

<210> 125  
<211> 251  
<212> PRT  
<213> Artificial sequence

<220>  
<223> scFv protein GMCC118

<400> 125

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Ser Phe Thr Asn Ala  
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

Gly Arg Ile Lys Ser Arg Asn Asp Gly Gly Ala Thr Asp Tyr Ala Ala  
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Asp Asp Thr Ala Val Tyr  
85 90 95

Tyr Cys Thr Thr Asp Asn Phe Pro Leu Arg Phe Leu Glu Trp Leu Ser  
100 105 110

His Pro Asp Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly  
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln  
130 135 140

Ala Val Leu Thr Gln Pro Ser Ser Val Ser Val Ser Pro Gly Gln Thr  
145 150 155 160

Val Thr Ile Thr Cys Ser Gly Glu Lys Leu Asp Asn Lys Tyr Ile Ser  
165 170 175

Trp Tyr Gln Gln Arg Pro Gly Arg Ser Pro Ile Leu Val Ile Tyr Gln  
 180 185 190

Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn  
 195 200 205

Ser Gly Asn Thr Ala Thr Leu Thr Ile Thr Gly Ser Gln Pro Leu Asp  
 210 215 220

Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Ala Trp Glu  
 225 230 235 240

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly  
 245 250

<210> 126

<211> 252

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMCC119

<400> 126

Glu Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Asn Tyr Thr Phe Thr Thr Tyr  
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Trp Ile Ser Thr Tyr Ser Gly Asn Thr Lys Tyr Ala Gln Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Ala Ala Tyr  
 65 70 75 80

Met Glu Leu Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys  
 85 90 95

Ala Arg Asp Ile Arg Val Trp Arg Gly Ser Gly Ser Val His Tyr Phe  
 100 105 110

Asp Pro Trp Gly Arg Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly  
 115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Ala  
 130 135 140

Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr  
 145 150 155 160

Ile Ser Cys Thr Gly Thr Ser Asn Asp Val Gly Gly Tyr Asn Phe Val  
 165 170 175

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Val Tyr  
 180 185 190

Asn Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser  
 195 200 205

Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu  
 210 215 220

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala His Ser Tyr Thr Leu  
 225 230 235 240

Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly  
 245 250

<210> 127  
 <211> 251  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMCC124

<400> 127

Gln Val Thr Leu Lys Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn  
 20 25 30

Ala Leu His Trp Val Arg Gln Ala Pro Gly Gln Arg Pro Glu Trp Met  
 35 40 45

Ala Trp Ile Asn Thr Ala Asn Gly Asn Thr Arg Tyr Ser Gln Lys Phe  
 50 55 60



Gln Gly Arg Leu Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Phe  
65 70 75 80

Met Asp Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Gln Lys Ala Tyr Lys Asn Tyr Tyr Tyr Tyr Tyr Gly Met Asp  
100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly  
115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Val  
130 135 140

Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile  
145 150 155 160

Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp  
165 170 175

Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Glu Asn  
180 185 190

Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gln Ser  
195 200 205

Gly Thr Ser Ala Thr Leu Gly Ile Ser Gly Leu Gln Thr Gly Asp Glu  
210 215 220

Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu Arg Ala Gly Val  
225 230 235 240

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly  
245 250

<210> 128

<211> 247

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMCC125

<400> 128

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr  
                   20                                  25                                  30

Ser Met His Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu  
                   35                                  40                                  45

Ser His Ile Gly Thr Ser Thr Ser Tyr Thr Asn Tyr Ala Asp Ser Val  
                   50                                  55                                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Phe Tyr  
                   65                                  70                                  75                                  80

Leu Gln Met Asn Ser Leu Arg Val Asp Asp Thr Ala Val Tyr Phe Cys  
                                   85                                  90                                  95

Ala Arg Gly Phe Gly Gly Leu Arg Gly Tyr Phe Asp Tyr Trp Gly Gln  
                                   100                                  105                                  110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly  
                   115                                  120                                  125

Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp  
                   130                                  135                                  140

Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Lys Ile Thr Cys Gln  
                   145                                  150                                  155                                  160

Gly Asp Arg Leu Arg Arg Phe Tyr Ala Ser Trp Tyr Gln Gln Lys Pro  
                                   165                                  170                                  175

Gly Gln Ala Pro Leu Leu Leu Ile Tyr Gly Lys Asn Ser Arg Pro Ser  
                                   180                                  185                                  190

Gly Ile Pro Asp Arg Phe Ser Gly Ser Thr Ser Gly Ala Thr Ala Ser  
                   195                                  200                                  205

Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys  
                   210                                  215                                  220

Asn Ser Arg Asp Ser Ser Gly Ser Leu His Ser Val Phe Gly Thr Gly  
                   225                                  230                                  235                                  240

Thr Lys Val Thr Val Leu Gly  
                                   245

<210> 129  
 <211> 246  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMCC126

<400> 129

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln  
 1 5 10 15

Thr Leu Ser Leu Ser Cys Ala Val Ser Gly Phe Ser Val Thr Ser Gly  
 20 25 30

His Tyr Trp Gly Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp  
 35 40 45

Ile Gly Asn Ile Tyr His Thr Gly Ser Thr Arg Tyr Asn Pro Ser Leu  
 50 55 60

Glu Ser Arg Val Ser Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser  
 65 70 75 80

Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Ile Tyr Tyr Cys  
 85 90 95

Ala Arg Val Gly Arg Gly Gln His Leu Val Arg Gly Asp Phe Asp Tyr  
 100 105 110

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
 115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr  
 130 135 140

Gln Pro Pro Ser Ile Ser Val Ser Pro Gly Gln Thr Ala Ser Ile Thr  
 145 150 155 160

Cys Ser Gly Asp Glu Leu Gly His Lys Tyr Ala Ser Trp Tyr Gln Gln  
 165 170 175

Lys Pro Gly Gln Ser Pro Val Val Val Val Tyr Gln Asp Asn Lys Arg  
 180 185 190

Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr  
 195 200 205

Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Val Asp Glu Ala Asp Tyr  
 210 215 220

Phe Cys Gln Ala Trp Asp Ser Ser Ala Val Val Phe Gly Gly Gly Thr  
 225 230 235 240

Lys Leu Thr Val Leu Gly  
 245

<210> 130  
 <211> 242  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMCC127

<400> 130

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Arg Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr  
 20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ser Gly Ile Asn Trp Asn Gly Gly Ser Thr Gly Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Arg Arg Tyr Ala Leu Asp Tyr Trp Gly Arg Gly Thr Leu Val  
 100 105 110

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser  
 130 135 140

Val Ala Leu Gly Gln Ala Val Arg Ile Thr Cys Gln Gly Asp Ser Leu  
145 150 155 160

Arg Thr Asn Tyr Ala Ser Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro  
165 170 175

Val Leu Val Ile Arg Gly Asn Asn Asn Arg Pro Ser Gly Ile Pro Asp  
180 185 190

Arg Phe Ser Gly Ser Asn Ser Gly Asp Thr Val Ser Leu Thr Ile Thr  
195 200 205

Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp  
210 215 220

Thr Ser Gly Tyr His Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val  
225 230 235 240

Leu Gly

<210> 131

<211> 246

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMCC129

<400> 131

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Ala Gln Pro Gly Gly  
1 5 10 15

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Asn Asn Tyr  
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

Ser Gly Ile Ser Ile Ser Gly Tyr Ser Thr Phe Tyr Thr Asp Ser Val  
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
65 70 75 80

Leu Gln Met Asn Ser Leu Gly Val Asp Asp Thr Ala Val Tyr Tyr Cys  
                     85                    90                    95

Ala Lys Arg Arg Gly Glu Gly Gly Asp Phe Asp Tyr Trp Gly Arg Gly  
                     100                    105                    110

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
                     115                    120                    125

Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp Pro  
                     130                    135                    140

Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly  
                     145                    150                    155                    160

Asp Ser Leu Arg Gly Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Ala Gly  
                     165                    170                    175

Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly  
                     180                    185                    190

Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu  
                     195                    200                    205

Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr  
                     210                    215                    220

Ser Arg Asp Arg Ser Gly Asn His Leu Gly Met Phe Gly Gly Gly Thr  
                     225                    230                    235                    240

Lys Val Thr Val Leu Gly  
                     245

<210> 132

<211> 248

<212> PRT

<213> Artificial sequence

<220>

<223> scFv protein GMCC131

<400> 132

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
                     1                    5                    10                    15

Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Arg Ser His  
                     20                    25                    30

Tyr Trp Ser Trp Met Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile  
           35                                  40                                  45

Gly Tyr Val Tyr Tyr Thr Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys  
           50                                  55                                  60

Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu  
   65                                  70                                  75                                  80

Asn Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Ile Tyr Tyr Cys Ala  
                                   85                                  90                                  95

Arg Phe Pro Tyr Ser Ser Gly Ser Asn Pro Leu Asp Tyr Trp Gly Arg  
                                   100                                  105                                  110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly  
           115                                  120                                  125

Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro  
           130                                  135                                  140

Ser Val Ser Ala Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly  
   145                                  150                                  155                                  160

Ser Ser Ser Asn Ile Gly Ala Arg Tyr Asp Val His Trp Tyr Gln His  
                                   165                                  170                                  175

Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asp Ser Asn Arg  
                                   180                                  185                                  190

Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser  
           195                                  200                                  205

Ala Ser Leu Ala Ile Thr Gly Leu Gln Pro Glu Asp Glu Ala Asp Tyr  
           210                                  215                                  220

Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Val Val Phe Gly Gly  
   225                                  230                                  235                                  240

Gly Thr Lys Val Thr Val Leu Gly  
                                   245

&lt;210&gt; 133

&lt;211&gt; 245

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; scFv protein GMCC136

&lt;400&gt; 133

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Ser Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Lys Cys Trp Arg Ser Gly Thr Ser Cys Pro Asp Gly Trp Gly Lys  
 100 105 110

Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 115 120 125

Gly Ser Gly Gly Gly Gly Ser Ala Leu Glu Ile Val Leu Thr Gln Ser  
 130 135 140

Pro Ala Thr Leu Ser Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys  
 145 150 155 160

Arg Thr Ser Gln Ser Val Gly Ser Lys Leu Ala Trp Tyr Gln Gln Lys  
 165 170 175

Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Thr Gly Ala  
 180 185 190

Thr Gly Asp Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe  
 195 200 205



Thr Leu Thr Ile Ser Asn Leu Gln Ser Glu Asp Leu Ala Ile Tyr Tyr  
 210 215 220

Cys Gln Gln Tyr His Lys Trp Pro Ile Thr Phe Gly Gln Gly Thr Arg  
 225 230 235 240

Leu Glu Ile Lys Arg  
 245

<210> 134  
 <211> 248  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMCC138

<400> 134

Glu Val Gln Leu Val Glu Thr Gly Pro Gly Leu Val Lys Pro Ser Gln  
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly  
 20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Val Pro Gly Lys Gly Leu Glu  
 35 40 45

Trp Ile Gly Tyr Asn Phe Tyr Asn Gly Ser Thr Tyr Phe Asn Pro Ser  
 50 55 60

Leu Lys Ser Arg Ala Thr Ile Ser Ile Asp Thr Thr Lys Asn Gln Phe  
 65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr  
 85 90 95

Cys Ala Arg Gly Asn Gly Tyr Arg Tyr Gly Arg Trp Phe Asp Pro Trp  
 100 105 110

Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly  
 115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Tyr Glu Leu Thr  
 130 135 140

Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Arg Ile Thr  
 145 150 155 160

Cys Ser Gly Asp Ala Leu Pro Lys Gln Tyr Ala Tyr Trp Tyr Gln Gln  
                           165                          170                          175

Lys Pro Gly Gln Ala Pro Val Leu Val Ile Ser Lys Asp Ser Glu Arg  
                           180                          185                          190

Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Ser Ser Gly Thr Thr  
                           195                          200                          205

Val Thr Leu Thr Ile Ser Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr  
                           210                          215                          220

Tyr Cys Gln Ser Ala Asp Ser Ser Gly Thr Tyr Trp Val Phe Gly Gly  
                           225                          230                          235                          240

Gly Thr Lys Val Thr Val Leu Gly  
                           245

<210> 135  
 <211> 246  
 <212> PRT  
 <213> Artificial sequence

<220>  
 <223> scFv protein GMCC142

<400> 135

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
   1                          5                          10                          15

Ser Val Thr Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ala Tyr  
                           20                          25                          30

Tyr Ile Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
                           35                          40                          45

Gly Met Ser Asn Pro Asn Gly Gly Tyr Thr Val Tyr Pro Pro Asn Phe  
                           50                          55                          60

Leu Gly Arg Val Thr Thr Thr Pro Asp Thr Ser Thr Asn Thr Ile Tyr  
                           65                          70                          75                          80

Met Glu Leu Arg Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
                           85                          90                          95



20	25	30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val		
35	40	45
Ala Val Ile Gly Phe Asp Gly Thr Thr Lys Tyr Tyr Val Asp Ser Val		
50	55	60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Ser		
65	70	75
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys		
85	90	95
Val Arg Glu Asp Tyr Tyr Tyr Asp Ser Ser Gly Tyr Tyr Phe Asp Tyr		
100	105	110
Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser		
115	120	125
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu		
130	135	140
Thr Gln Asp Pro Phe Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile		
145	150	155
Ala Cys Arg Gly Asp Ser Leu Arg Asp Ser Tyr Ala Ser Trp Tyr Gln		
165	170	175
Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Val Tyr Gly Asn Asn Leu		
180	185	190
Arg Pro Ser Gly Ile Pro Gly Arg Xaa Ser Gly Phe Ser Ser Gly Asp		
195	200	205
Thr Ser Ser Leu Ala Ile Thr Glu Thr Gln Ala Gly Asp Glu Ala Asp		
210	215	220
Tyr Tyr Cys Ser Ser Arg Gly Asn Ser Thr Ser Arg Leu Tyr Val Phe		
225	230	235
Gly Thr Gly Thr Lys Leu Thr Val Leu Gly		
245	250	

&lt;210&gt; 137

<211> 747  
 <212> DNA  
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<220>  
 <221> CDS  
 <222> (1)..(747)  
 <223> Polynucleotide encoding GMBC603 scFv protein

<400> 137

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cag gtc cag ctg gta cag tct ggg gga ggt gtg gta cgg cct ggg ggg      48
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1          5          10          15

tcc ctg aga ctc tcc tgt gca gcc tct gga ttc aca ttt gat gat tat      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
          20          25          30

ggc atg agc tgg gtc cgc caa gct cca ggg aag ggg ctg gag tgg gtc      144
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45

tct ggt att aat tgg aat ggt ggt agc aca ggt tat gca gac tct gtg      192
Ser Gly Ile Asn Trp Asn Gly Gly Ser Thr Gly Tyr Ala Asp Ser Val
          50          55          60

aag ggc cga ttc acc atc tcc aga gac aac gcc aag aac tcc ctc tat      240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
          65          70          75          80

ctc caa atg aac agt ctg aga gct gag gac acc gcc ttg tat tac tgt      288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
          85          90          95

gca aaa gat ctg aat tac gat ttt tgg agt ggt tcc ggt atg gac gtc      336
Ala Lys Asp Leu Asn Tyr Asp Phe Trp Ser Gly Ser Gly Met Asp Val
          100          105          110

tgg ggc cga gga acc ctg gtc acc gtc tcc tca ggt gga ggc ggt tca      384
Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
          115          120          125

ggc gga ggt ggc agc ggc ggt ggc gga tgc cag tct gtg ctg act cag      432
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln
          130          135          140

cct gcc tcc gtg tct ggg tct cct gga cag tgc atc acc atc tcc tgc      480
Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys
          145          150          155          160

act gga acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac      528
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr
          165          170          175

caa caa cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt      576
Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser
          180          185          190

aag cgg ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc      624

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Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly  
 195 200 205  
 aac acg gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct 672  
 Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala  
 210 215 220  
 gat tat tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc 720  
 Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly  
 225 230 235 240  
 gga ggg acc aag ctg acc gtc cta ggt 747  
 Gly Gly Thr Lys Leu Thr Val Leu Gly  
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 <210> 138  
 <211> 729  
 <212> DNA  
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 <222> (1)..(729)  
 <223> Polynucleotide encoding GMBC604 scFv protein  
 <400> 138  
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 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu  
 1 5 10 15  
 tcc ctg agg atc tca tgt aag ggt tct gga tac acc ttt acc aac tac 96  
 Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr  
 20 25 30  
 tgg atc aac tgg gtg cgc cag gtg ccc gga aaa ggc ctg gag tgg atg 144  
 Trp Ile Asn Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Met  
 35 40 45  
 ggg atg att gat cct act gac tct tat gcc aaa tac agc ccg tcc ttc 192  
 Gly Met Ile Asp Pro Thr Asp Ser Tyr Ala Lys Tyr Ser Pro Ser Phe  
 50 55 60  
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 Gln Gly His Val Thr Ile Ser Thr Asp Lys Ser Val Ser Thr Ala Tyr  
 65 70 75 80  
 ctg cag tgg aga agc ctg cag gcc tcg gac agc gcc ata tat tat tgt 288  
 Leu Gln Trp Arg Ser Leu Gln Ala Ser Asp Ser Ala Ile Tyr Tyr Cys  
 85 90 95  
 gtg agg gga tac agt tat gac ctt gac tac tgg ggc aag gga acc ctg 336  
 Val Arg Gly Tyr Ser Tyr Asp Leu Asp Tyr Trp Gly Lys Gly Thr Leu  
 100 105 110  
 gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga ggt ggc agc ggc 384  
 Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly  
 115 120 125  
 ggt ggc gga tcg cag tct gtg ctg act cag cct gcc tcc gtg tct ggg 432

Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser Gly  
 130 135 140

tct cct gga cag tcg atc acc atc tcc tgc act gga acc agc agt gac 480  
 Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp  
 145 150 155 160

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 Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys  
 165 170 175

gcc ccc aaa ctc atg att tat gag ggc agt aag cgg ccc tcg ggg gtt 576  
 Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser Gly Val  
 180 185 190

tct aat cgc ttc tct ggc tcc aag tct ggc aac acg gcc tcc ctg aca 624  
 Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205

atc tct ggg ctc cag gct gag gac gag gct gat tat tac tgc agc tca 672  
 Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser  
 210 215 220

tat aca acc agg agc act cga gtt ttc ggc gga ggg acc aag ctg acc 720  
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 225 230 235 240

gtc cta ggt 729  
 Val Leu Gly

<210> 139  
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<220>  
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<400> 139

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tcc ctt aga ctc tcc tgt gaa acc tct ggt ttc aaa ttc agt gac gcc 96  
 Ser Leu Arg Leu Ser Cys Glu Thr Ser Gly Phe Lys Phe Ser Asp Ala  
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tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gct gca 192  
 Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80  
 ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 aga ggc acc ctg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga 384  
 Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tgc cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140  
 tcc gtg tct ggg tct cct gga cag tgc atc acc atc tcc tgc act gga 480  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
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 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
 245  
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Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	
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ggc	atg	cac	tgg	gtc	cgc	cag	gct	cca	ggc	aag	ggg	ctg	gag	tgg	gtg	144
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
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gca	ttt	ata	cgg	tat	gat	gga	agt	aat	aaa	tac	tat	gca	gac	tcc	gtg	192
Ala	Phe	Ile	Arg	Tyr	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	
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Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	
65			70			75										
ctg	caa	atg	aac	agc	ctg	aga	gct	gag	gac	acg	gct	gtg	tat	tac	tgt	288
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
85			90			95										
gcg	aaa	tcc	tcg	tcc	ttt	gcc	aat	gct	ttt	gat	atc	tgg	ggc	caa	gga	336
Ala	Lys	Ser	Ser	Ser	Phe	Ala	Asn	Ala	Phe	Asp	Ile	Trp	Gly	Gln	Gly	
100			105			110										
acc	acg	gtc	acc	gtc	tcc	tca	ggg	gga	ggc	ggg	tca	ggc	gga	ggg	ggc	384
Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	
115			120			125										
agc	ggc	ggg	ggc	gga	tcg	tct	gag	ctg	act	cag	gac	cct	gct	gtg	tct	432
Ser	Gly	Gly	Gly	Gly	Ser	Ser	Glu	Leu	Thr	Gln	Asp	Pro	Ala	Val	Ser	
130			135			140										
gtg	gcc	ttg	gga	cag	aca	gtc	agg	atc	aca	tgc	caa	gga	gac	agc	ctc	480
Val	Ala	Leu	Gly	Gln	Thr	Val	Arg	Ile	Thr	Cys	Gln	Gly	Asp	Ser	Leu	
145			150			155										
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Arg	Ser	Tyr	Tyr	Ala	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	
165			170			175										
gta	ctt	gtc	atc	tat	ggg	aaa	aac	aac	cgg	ccc	tca	ggg	atc	cca	gac	576
Val	Leu	Val	Ile	Tyr	Gly	Lys	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Asp	
180			185			190										
cga	ttc	tct	ggc	tcc	agc	tca	gga	aac	aca	gct	tcc	ttg	acc	atc	act	624
Arg	Phe	Ser	Gly	Ser	Ser	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Thr	
195			200			205										
ggg	gct	cag	gcg	gaa	gat	gag	gct	gac	tat	tac	tgt	aac	tcc	cgg	gac	672
Gly	Ala	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Asn	Ser	Arg	Asp	
210			215			220										
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Leu Gly

&lt;210&gt; 141

&lt;211&gt; 741

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1) .. (741)

&lt;223&gt; Polynucleotide encoding GMBC607 scFv protein

&lt;400&gt; 141

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Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1          5          10          15

tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala
          20          25          30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc      144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gct gca      192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala
          50          55          60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac atg      240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Met
          65          70          75          80

ctg tat ctg gaa atg aac agt ctg aaa acc gag gac aca gcc ctg tat      288
Leu Tyr Leu Glu Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr
          85          90          95

tac tgt acg tgg gac tgg gat ttc tat tac ggt atg aac gtc tgg ggc      336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly
          100          105          110

caa ggg aca atg gtc acc gtc tct tca ggt gga ggc ggt tca ggc gga      384
Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
          115          120          125

ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc      432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala
          130          135          140

tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga      480
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly
          145          150          155          160

acc agc agt gac gtt ggt gat tat aac tat gtc tcc tgg tac caa caa      528
Thr Ser Ser Asp Val Gly Asp Tyr Asn Tyr Val Ser Trp Tyr Gln Gln
          165          170          175

cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg      576

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His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg
      180                      185                      190

ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg      624
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
      195                      200                      205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat      672
Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
      210                      215                      220

tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg      720
Tyr Cys Ser Ser Tyr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly
      225                      230                      235                      240

acc aag ctg acc gtc cta ggt      741
Thr Lys Leu Thr Val Leu Gly
      245

<210> 142
<211> 738
<212> DNA
<213> Artificial sequence

<220>
<221> CDS
<222> (1)..(738)
<223> Polynucleotide encoding GMBC608 scFv protein

<400> 142

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Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1                      5                      10                      15

tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt agt gac tcc      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
      20                      25                      30

tac atg acc tgg atc cgc cag gct cca ggg gag ggg ctg gag ttt gtt      144
Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Glu Gly Leu Glu Phe Val
      35                      40                      45

tca tat att agt agt ggt agt agt acc act tac tat aca gac tct gtg      192
Ser Tyr Ile Ser Ser Gly Ser Ser Thr Thr Tyr Tyr Thr Asp Ser Val
      50                      55                      60

aag ggc cga ttc acc atc tcc agg gac aat tcc aaa aac act ctg tat      240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
      65                      70                      75                      80

cta caa atg aac agc ctg aga cct gag gac acg gct gtg tat tac tgt      288
Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
      85                      90                      95

gcg agg aga agc atc tcg tcc gac tac tac tcc tac tac ttg gac gtc      336
Ala Arg Arg Ser Ile Ser Ser Asp Tyr Tyr Ser Tyr Tyr Leu Asp Val
      100                      105                      110

tgg ggc aag gga acc ctg gtc acc gtc tcc tca ggt gga ggc ggt tca      384

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Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
 115 120 125  
 ggc gga ggt ggc agc ggc ggt ggc gga tcg tct gag ctg act cag gac 432  
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp  
 130 135 140  
 cct gct gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa 480  
 Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln  
 145 150 155 160  
 gga gac agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca 528  
 Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro  
 165 170 175  
 gga cag gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca 576  
 Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser  
 180 185 190  
 ggg atc cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc 624  
 Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser  
 195 200 205  
 ttg acc atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt 672  
 Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys  
 210 215 220  
 aac tcc cgg gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc 720  
 Asn Ser Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr  
 225 230 235 240  
 aag ctg acc gtc cta ggt 738  
 Lys Leu Thr Val Leu Gly  
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 <222> (1)..(741)  
 <223> Polynucleotide encoding GMBC609 scFv protein  
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 tca ctg aga ctc tcc tgt gaa gcc tct gga ttc gaa ttt aat tat gcc 96  
 Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Glu Phe Asn Tyr Ala  
 20 25 30  
 tgg atg agt tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtt 144  
 Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgt agt aga agc gaa gct agt ggt ggg aca aca gac tac gct gca 192

Gly	Arg	Ser	Arg	Ser	Glu	Ala	Ser	Gly	Gly	Thr	Thr	Asp	Tyr	Ala	Ala		
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Pro	Leu	Gln	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr		
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ctg	tat	cta	caa	gtc	aac	agc	ctg	aaa	atc	gag	gac	aca	ggc	gtg	tat	288	
Leu	Tyr	Leu	Gln	Val	Asn	Ser	Leu	Lys	Ile	Glu	Asp	Thr	Gly	Val	Tyr		
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ttc	tgt	aag	tgg	gag	aaa	tca	gag	tac	tac	ggt	atg	gac	gtc	tgg	ggc	336	
Phe	Cys	Lys	Trp	Glu	Lys	Ser	Glu	Tyr	Tyr	Gly	Met	Asp	Val	Trp	Gly		
			100					105					110				
cgg	gga	acc	ccg	gtc	acc	gtc	tcc	tca	ggt	gga	ggc	ggt	tca	ggc	gga	384	
Arg	Gly	Thr	Pro	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly		
			115				120						125				
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Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ser	Val	Leu	Thr	Gln	Pro	Pro		
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Ser	Val	Ser	Ala	Ala	Pro	Gly	Gln	Lys	Val	Thr	Ile	Ser	Cys	Ser	Gly		
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agc	acc	tcc	aac	att	ggg	aat	aat	tat	gtc	tcc	tgg	tac	caa	cag	cac	528	
Ser	Thr	Ser	Asn	Ile	Gly	Asn	Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln	His		
				165				170						175			
cca	ggc	aaa	gcc	ccc	aaa	ctc	atg	att	tat	gat	gtc	agt	aag	cgg	ccc	576	
Pro	Gly	Lys	Ala	Pro	Lys	Leu	Met	Ile	Tyr	Asp	Val	Ser	Lys	Arg	Pro		
			180					185					190				
tca	ggg	gtc	cct	gac	cga	ttc	tct	ggc	tcc	aag	tct	ggc	aac	tca	gcc	624	
Ser	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Lys	Ser	Gly	Asn	Ser	Ala		
			195				200					205					
tcc	ctg	gac	atc	agt	ggg	ctc	cag	tct	gag	gat	gag	gct	gat	tat	tac	672	
Ser	Leu	Asp	Ile	Ser	Gly	Leu	Gln	Ser	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr		
			210				215					220					
tgt	gca	gca	tgg	gat	gac	agc	ctg	agt	gaa	ttt	ctc	ttc	gga	act	ggg	720	
Cys	Ala	Ala	Trp	Asp	Asp	Ser	Leu	Ser	Glu	Phe	Leu	Phe	Gly	Thr	Gly		
			225			230			235				240				
acc	aag	ctg	acc	gtc	cta	ggt										741	
Thr	Lys	Leu	Thr	Val	Leu	Gly											
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<210> 144  
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<220>  
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Ser Val Lys Val Ser Cys Lys Thr Ser Gly Phe Thr Phe Gly Ala Tyr	
20 25 30	
tac atc cac tgg gtg cga cag gtc cct gga caa ggg ctt gag tgg atg	144
Tyr Ile His Trp Val Arg Gln Val Pro Gly Gln Gly Leu Glu Trp Met	
35 40 45	
gga tgg atc gac cct aac aat ggt ggc aca aac tat gca cag aaa ttt	192
Gly Trp Ile Asp Pro Asn Asn Gly Gly Thr Asn Tyr Ala Gln Lys Phe	
50 55 60	
cag ggc agg gtc acc atg acc agg gac atg tcc acc acc aca acc tac	240
Gln Gly Arg Val Thr Met Thr Arg Asp Met Ser Thr Thr Thr Tyr	
65 70 75 80	
atg gag gtc agt ggg cta cat tct gac gac acg gcc gtg tat tac tgt	288
Met Glu Val Ser Gly Leu His Ser Asp Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg agg gcc aga gtg gcg aca atc ctt gaa tat tgg ggc agg ggc acc	336
Ala Arg Ala Arg Val Ala Thr Ile Leu Glu Tyr Trp Gly Arg Gly Thr	
100 105 110	
ctg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga ggt ggc agc	384
Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser	
115 120 125	
ggc ggt ggc gga tcg cct gag ctg act cag gac cct gct gtg tct gtg	432
Gly Gly Gly Gly Ser Pro Glu Leu Thr Gln Asp Pro Ala Val Ser Val	
130 135 140	
gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac agc ctc aga	480
Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg	
145 150 155 160	
agc tat tat gca agc tgg tac cag cag aag cca gga cag gcc cct gta	528
Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val	
165 170 175	
ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc cca gac cga	576
Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg	
180 185 190	
ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc atc act ggg	624
Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly	
195 200 205	
gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc cgg gac agc	672
Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser	
210 215 220	
agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg acc gtc cta	720

Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu  
 225 230 235 240

ggt  
 Gly

723

<210> 145  
 <211> 717  
 <212> DNA  
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 <223> Polynucleotide encoding GMBC612 scFv protein

<400> 145

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 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Tyr  
 20 25 30

ggc atg caa tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg 144  
 Gly Met Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

gca ttt ata cgg tat gat gga agt att aaa tac tat gca gac tcc gtg 192  
 Ala Phe Ile Arg Tyr Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

aag ggc cga ttc acc gtc tcc aga gac aac tcc aag aac acg ctg tat 240  
 Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

ctg caa atg aac agc ctg aga gcc gag gac acg gct gtc tat tac tgt 288  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aga ggt tat cga atc gtt gac tac tgg ggc caa gga acc ctg gtc 336  
 Ala Arg Gly Tyr Arg Ile Val Asp Tyr Trp Gly Gln Gly Thr Leu Val  
 100 105 110

acc gtc tcc tca ggt gga ggc ggt tca ggc gga ggt ggc agc ggc ggt 384  
 Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

ggc gga tcg gac atc cag atg acc cag tct cct tcc acc ctg tcc cca 432  
 Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Pro  
 130 135 140

tct att gga gac aga gtc acc atc acc tgc cgg gcc agt gag ggt att 480  
 Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile  
 145 150 155 160

tat cac tgg ttg gcc tgg tat cag cag aag cca ggg aaa gcc cct aaa 528

Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys  
 165 170 175  
 ctc ctg atc tat aag gcc tct agt tta gcc agt ggg gcc cca tca agg 576  
 Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser Arg  
 180 185 190 /  
 ttc agc ggc agt gga tct ggg aca gat ttc act ctc acc atc agc agc 624  
 Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser  
 195 200 205  
 ctg cag cct gat gat ttt gca act tat tac tgc caa caa tat agt aat 672  
 Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asn  
 210 215 220  
 tat ccg ctc act ttc ggc gga ggg acc aag ctg gag atc aaa cgt 717  
 Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg  
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 Lys Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly  
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 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Ser His  
 20 25 30  
 tgg atg agc tgg gtc cgc cag gct ccg ggg aag ggg ctg gag tgg gtg 144  
 Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 gcc agt ata aag caa gat gga cgt gag aaa cac ttt gtg gat tct gtg 192  
 Ala Ser Ile Lys Gln Asp Gly Arg Glu Lys His Phe Val Asp Ser Val  
 50 55 60  
 aag ggc cga ttc agc atc tcc aga gac aac gcc aag aac tca ctg tat 240  
 Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr  
 65 70 75 80  
 ctg caa atg aac agc ctg aga acc gag gac acg gct gtc tac tac tgt 288  
 Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aga gag acg tac ggg gga tac tac tat tac ttc atg gac gtc tgg 336  
 Ala Arg Glu Thr Tyr Gly Gly Tyr Tyr Tyr Tyr Phe Met Asp Val Trp  
 100 105 110  
 ggc aaa gga acc ctg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc 384



Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly  
 115 120 125  
 gga ggt ggc agc ggc ggt ggc gga tcg tct gag ctg act cag gac cct 432  
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro  
 130 135 140  
 gct gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga 480  
 Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly  
 145 150 155 160  
 gac agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga 528  
 Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly  
 165 170 175  
 cag gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg 576  
 Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly  
 180 185 190  
 atc cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg 624  
 Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu  
 195 200 205  
 acc atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac 672  
 Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn  
 210 215 220  
 tcc cgg gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag 720  
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 225 230 235 240  
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 Leu Thr Val Leu Gly  
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 tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30  
 tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca 192

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
 Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

cga ggg aca atg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga 384  
 Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc 432  
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 130 135 140

tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga 480  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
 245

<210> 148  
 <211> 741  
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<220>  
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 <222> (1)..(741)  
 <223> Polynucleotide encoding GMBC615 scFv protein

&lt;400&gt; 148

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly	
1 5 10 15	
tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc aaa ttc agt gac gcc	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Asp Ala	
20 25 30	
tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gct gca	192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
aaa ggc acc ctg gtc gcc gtc tcc tca ggt gga ggc ggt tca ggc gga	384
Lys Gly Thr Leu Val Ala Val Ser Ser Gly Gly Gly Gly Ser Gly Gly	
115 120 125	
ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc	432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala	
130 135 140	
tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga	480
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa	528
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg	576
His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg	
180 185 190	
ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg	624
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr	
195 200 205	
gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat	672
Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr	
210 215 220	
tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg	720

Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
 245

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<400> 149

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 1 5 10 15

tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

ggc cgt att aaa agt aaa ggt agt ggt ggg aca aca gac tac gct gca 192  
 Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

ccc gtg aaa gac aga ttc acc atc tca aga gat gat tca gaa aac acg 240  
 Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asn Thr  
 65 70 75 80

ctg tat cta caa atg aac agc ctg aaa acc gag gac aca gcc gta tat 288  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr  
 85 90 95

tac tgt acg tgg gac cat agt tat tat tat gat atg gcc gtc tgg ggc 336  
 Tyr Cys Thr Trp Asp His Ser Tyr Tyr Tyr Asp Met Ala Val Trp Gly  
 100 105 110

cgg gga acc ctg gtc acc gtc tcc tca ggt gga ggc ggc tca ggc gga 384  
 Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct ccc 432  
 Gly Gly Ser Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro  
 130 135 140

ttc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga 480  
 Phe Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
165 170 175

cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
180 185 190

ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
195 200 205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
210 215 220

tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
225 230 235 240

acc aag ctg acc gtc cta ggt 741  
Thr Lys Leu Thr Val Leu Gly  
245

<210> 150  
<211> 729  
<212> DNA  
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<222> (1)..(729)  
<223> Polynucleotide encoding GMBC617 scFv protein

<400> 150

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1 5 10 15

tcc ctg aga ctc tcc tgt gca gcc tct ggg ttc acc gtc agt agc aac 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn  
20 25 30

tac atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

tca gtt att tat agc ggt ggt agc aca tac tac gca gac tcc gtg aag 192  
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys  
50 55 60

ggc cga ttc acc atc tcc aga cac aat tcc aag aac acg ctg tat ctt 240  
Gly Arg Phe Thr Ile Ser Arg His Asn Ser Lys Asn Thr Leu Tyr Leu  
65 70 75 80

caa atg aac agc ctg aga gct gag gac acg gcc gtg tat tac tgt gcg 288  
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala  
85 90 95

aga ggt cta tgg ttc ggg gag tta ttg tac tgg ggc cag ggc acc ctg 336

Arg Gly Leu Trp Phe Gly Glu Leu Leu Tyr Trp Gly Gln Gly Thr Leu  
 100 105 110  
 gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga ggt ggc agc ggc 384  
 Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
 115 120 125  
 ggt ggc gga tcg cag tct gcc ctg act cag cct gcc tcc gtg tct gga 432  
 Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly  
 130 135 140  
 tct cgt gga cag tcg atc acc atc tcc tgc act gga acc act ggt gac 480  
 Ser Arg Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Thr Gly Asp  
 145 150 155 160  
 gtt ggt ggt tat gac tat gtc tcc tgg tac caa cag cac cca ggc aaa 528  
 Val Gly Gly Tyr Asp Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys  
 165 170 175  
 gcc ccc aaa ctc ctc atc tat ggt aac agc aat cgg ccc tca ggc gtc 576  
 Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val  
 180 185 190  
 cct gat cgc ttc tct gcc tcc aag tcc ggc aat acg gcc tcc ctg acc 624  
 Pro Asp Arg Phe Ser Ala Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205  
 atc tct gga ctc cag gct gag gat gag gct gat tat ttc tgc agc aca 672  
 Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Phe Cys Ser Thr  
 210 215 220  
 tat gca ccc ccc ggt att att atg ttc ggc gga ggc acc aag ctg acc 720  
 Tyr Ala Pro Pro Gly Ile Ile Met Phe Gly Gly Gly Thr Lys Leu Thr  
 225 230 235 240  
 gtc cta ggt 729  
 Val Leu Gly  
  
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 <223> Polynucleotide encoding GMBC618 scFv protein  
  
 <400> 151  
  
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 Glu Val Gln Leu Val Gln Ser Gly Gly Leu Val Lys Pro Gly Gly  
 1 5 10 15  
 tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc aaa ttc gat gac gcc 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Asp Asp Ala  
 20 25 30  
 tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt att aaa agc aaa cgt agt ggt ggg aca ata gac tac gct gca	192
Gly Arg Ile Lys Ser Lys Arg Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat ctg caa atg aat agt ctg aga acc gag gac aca gcc ttg tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
aga ggc acc ctg gtc acc gtc tcc tca ggc gga ggc ggt tca ggc gga	384
Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
ggc ggc agc ggc ggt ggc gga tgc cag tct gtg ctg act cag cca ccc	432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro	
130 135 140	
tca gcg tct ggg acc ccc ggg cag agg gtc acc atc tct tgt tct gga	480
Ser Ala Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly	
145 150 155 160	
agc agc tcc aac atc ggg agt aac act gta aac tgg tac cag cga ctc	528
Ser Ser Ser Asn Ile Gly Ser Asn Thr Val Asn Trp Tyr Gln Arg Leu	
165 170 175	
cca gga gcg gcc ccc caa ctc ctc atc tac aat aat gac cag cgg ccc	576
Pro Gly Ala Ala Pro Gln Leu Leu Ile Tyr Asn Asn Asp Gln Arg Pro	
180 185 190	
tca ggg atc cct gac cga ttc tct ggc tcc aag tct ggc acc tca ggc	624
Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Gly	
195 200 205	
tcc ctg gtc atc agt ggg ctc cag tct gaa gat gag gct gat tac tac	672
Ser Leu Val Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr	
210 215 220	
tgt gcg tca tgg gat gac agt ctg aat ggt cgg gtg ttc ggc gga ggg	720
Cys Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val Phe Gly Gly Gly	
225 230 235 240	
acc aag ctg acc gtc cta ggt	741
Thr Lys Leu Thr Val Leu Gly	
245	

&lt;210&gt; 152

&lt;211&gt; 732

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(732)

&lt;223&gt; Polynucleotide encoding GMBC619 scFv protein

&lt;400&gt; 152

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg	
1 5 10 15	
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttc agg agc tat	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Tyr	
20 25 30	
ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg	144
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
gca gtt ata aca tat gat gga agt aat aaa tac tat gca gac tcc gtg	192
Ala Val Ile Thr Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val	
50 55 60	
aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat	240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	
65 70 75 80	
ctg caa atg aac agc ctg aga gct gac gac acg gct gtg tat tac tgt	288
Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aga gat ggg ggt ggc tgg tac cac ccg agg ctt gac tac tgg ggc	336
Ala Arg Asp Gly Gly Gly Trp Tyr His Pro Arg Leu Asp Tyr Trp Gly	
100 105 110	
caa ggg aca atg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga	384
Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
ggt ggc agc ggc ggt ggc gga tcg tct gag ctg act cag gac cct gct	432
Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala	
130 135 140	
gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac	480
Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp	
145 150 155 160	
agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga cag	528
Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln	
165 170 175	
gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc	576
Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile	
180 185 190	
cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc	624
Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr	
195 200 205	
atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc	672



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Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser
 210                               215                               220

cgg gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg      720
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acc gtc cta ggt      732
Thr Val Leu Gly

<210> 153
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<220>
<221> CDS
<222> (1)..(741)
<223> Polynucleotide encoding GMBC620 scFv protein

<400> 153

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tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala
20                               25                               30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc      144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35                               40                               45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gcg      192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala
50                               55                               60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg      240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                               70                               75                               80

ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat      288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr
85                               90                               95

tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc      336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly
100                               105                               110

cgg ggg aca atg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga      384
Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
115                               120                               125

ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc      432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala
130                               135                               140

tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga      480

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 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
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tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
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ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg 144  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

gca gtt ata tca tat gat gga agt aat aaa tac tat gca gac tcc gtg 192  
 Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60

aag ggc cga ttc acc atc tcc aga gac aat tcc aag aat acg ctg tat 240  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

ctg caa atg gac agc ctg aga gcc gag gac acg gcc gta tat ttc tgt 288

Leu Gln Met Asp Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys  
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 gcg aaa aga ggt cta tgg acg cca att gac tac tgg ggc aaa gga acc 336  
 Ala Lys Arg Gly Leu Trp Thr Pro Ile Asp Tyr Trp Gly Lys Gly Thr  
 100 105 110  
 ctg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga ggt ggc agc 384  
 Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser  
 115 120 125  
 ggc ggt ggc gga tcg tct gag ctg act cag gac cct gct gtg tct gtg 432  
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 165 170 175  
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 Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg  
 180 185 190  
 ttc tct ggc tcc aac tca gga aac aca gct tcc ttg acc atc act ggg 624  
 Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly  
 195 200 205  
 gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc cgg gac agc 672  
 Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser  
 210 215 220  
 agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg acc gtc cta 720  
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Gly Arg Ile Lys Ser Lys Arg Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
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ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa gac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asp Thr	
65 70 75 80	
atg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat	288
Met Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
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Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
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Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly	
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Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
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Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
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His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg	
180 185 190	
ccc tca ggg gtt tct aat cgc ttc ttt ggc tcc aag tct ggc aac acg	624
Pro Ser Gly Val Ser Asn Arg Phe Phe Gly Ser Lys Ser Gly Asn Thr	
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Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr	
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Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly	
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acc aag ctg acc gtc cta ggt	741
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tgg atg agt tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtt	144
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ggc cgt agt aga agc gaa gct agt ggt ggg aca aca gac tac gct gca	192
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50 55 60	
ccc ctg caa gac aga ttc acc atc tca aga gat gat tca aaa aac aca	240
Pro Leu Gln Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat cta caa gtc aac agc ctg aaa atc gag gac aca ggc gtg tat	288
Leu Tyr Leu Gln Val Asn Ser Leu Lys Ile Glu Asp Thr Gly Val Tyr	
85 90 95	
ttc tgt aag tgg gag aaa tca gag tac tac ggt atg gac gtc tgg ggc	336
Phe Cys Lys Trp Glu Lys Ser Glu Tyr Tyr Gly Met Asp Val Trp Gly	
100 105 110	
cgg gga acc ccg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga	384
Arg Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly	
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Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala	
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Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa	528
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aag gcc ccc aaa ctc atg att tat gag ggc agt aag cgg	576
His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg	
180 185 190	
ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg	624

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
195 200 205

gcc tcc ctg aca atc tct ggg ctc cgg gct gag gac gag gct gat tat 672  
Ala Ser Leu Thr Ile Ser Gly Leu Arg Ala Glu Asp Glu Ala Asp Tyr  
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tac tgc agc tca tat aca acc aag agc act caa gtt ttc ggc gga ggg 720  
Tyr Cys Ser Ser Tyr Thr Thr Lys Ser Thr Gln Val Phe Gly Gly Gly  
225 230 235 240

acc aag ctg acc gtc cta ggt 741  
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Ser Val Arg Val Ser Cys Lys Ala Ser Arg Tyr Ile Phe Ser Asn Tyr  
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Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
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50 55 60

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Gln Asp Arg Leu Thr Met Thr Thr Asp Thr Ser Thr Asn Thr Val Phe  
65 70 75 80

atg gag ctg agg agc ctg agt tct gac gac acg gcc gtg tat tac tgt 288  
Met Glu Leu Arg Ser Leu Ser Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

gcg agt gcc ccc tac tat tac ggt atg ggc atc tgg ggc aag gga acc 336  
Ala Ser Ala Pro Tyr Tyr Tyr Gly Met Gly Ile Trp Gly Lys Gly Thr  
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ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga ggt ggc agc 384  
Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser  
115 120 125

ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc tcc gtg tct 432

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser  
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 145 150 155 160  
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 Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly  
 165 170 175  
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 Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Gly Asn Arg Pro Ser Gly  
 180 185 190  
 gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg gcc tcc ctg 624  
 Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu  
 195 200 205  
 aca atc tct ggg ctc cag gct gag gac gag gct gat tat tac tgc agc 672  
 Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser  
 210 215 220  
 tca tat aca acc agg agc act cga gtt ttc ggc gga ggg acc aag ctg 720  
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 Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr  
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 Gly Trp Ile Ser Ala Tyr Lys Gly Asn Ala Asn Tyr Ala Glu Lys Phe  
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Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Asn Thr Ala Tyr	
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85 90 95	
gcg aga act cgg ata tca gtg gct ggc cta gac tac tac tac tac ggt	336
Ala Arg Thr Arg Ile Ser Val Ala Gly Leu Asp Tyr Tyr Tyr Tyr Gly	
100 105 110	
ttg gac gtc tgg ggg agg gga acc ctg gtc acc gtc tcc tca ggt gga	384
Leu Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly	
115 120 125	
ggc ggt tca ggc gga ggt ggc agc ggc ggt ggc gga tcc tct gag ctg	432
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu	
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145 150 155 160	
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Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Thr Asn Trp Phe Gln	
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180 185 190	
cgg ccc tca ggg atc cca gac cga ttc tct ggc tcc agc tca gga aac	624
Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn	
195 200 205	
aca gct tcc ttg acc atc act ggg gct caa gcg gaa gat gag gct gac	672
Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp	
210 215 220	
tat tac tgt aac tcc cgg gac agc agt ggt aac cat gtg gta ttc ggc	720
Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Val Val Phe Gly	
225 230 235 240	
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Ser	Leu	Arg	Leu	Ser	Cys	Ala	Gly	Ser	Gly	Phe	Lys	Phe	Ser	Asp	Ala	
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Trp	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
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Pro	Val	Lys	Asp	Arg	Phe	Ile	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asp	Thr	
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Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Leu	Tyr	
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Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	
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Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ser	Glu	Leu	Thr	Gln	Asp	Pro	Ala	
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gtg	tct	gtg	gcc	ttg	gga	cag	aca	gtc	agg	atc	act	tgc	caa	gga	gac	480
Val	Ser	Val	Ala	Leu	Gly	Gln	Thr	Val	Arg	Ile	Thr	Cys	Gln	Gly	Asp	
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agt	ctc	aga	agc	tat	tac	aca	aac	tgg	ttc	cag	cag	aag	cca	gga	cag	528
Ser	Leu	Arg	Ser	Tyr	Tyr	Thr	Asn	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Gln	
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Ala	Pro	Leu	Leu	Val	Val	Tyr	Ala	Lys	Asn	Lys	Arg	Pro	Ser	Gly	Ile	
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cca	gac	cga	ttc	tct	ggc	tcc	agc	tca	gga	aac	aca	gct	tcc	ttg	acc	624
Pro	Asp	Arg	Phe	Ser	Gly	Ser	Ser	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	
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atc	act	ggg	gct	cag	gcg	gaa	gat	gag	gct	gac	tat	tac	tgt	cat	tcc	672
Ile	Thr	Gly	Ala	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	His	Ser	
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Arg	Asp	Ser	Ser	Gly	Asn	His	Val	Leu	Phe	Gly	Gly	Gly	Thr	Lys	Leu	
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Thr Val Leu Gly

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	
65 70 75 80	
ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt	288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aag gct act tct ttg cta aat gct ttt gat atc tgg ggc cgg gga	336
Ala Lys Ala Thr Ser Leu Leu Asn Ala Phe Asp Ile Trp Gly Arg Gly	
100 105 110	
acc atg gtc acc gtc tct tca ggt gga ggc ggt tca ggc gga ggt ggc	384
Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly	
115 120 125	
agc ggc ggt ggc gga tgc tct gag ctg act cag gac cct gct gtg tct	432
Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser	
130 135 140	
gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac agc ctc	480
Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu	
145 150 155 160	
aga agc tat tat gca agc tgg tac cag cag aag cca gga cag gcc cct	528
Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro	
165 170 175	
gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc cca gac	576

Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp  
180 185 190

cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc atc act 624  
Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr  
195 200 205

ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc cgg gac 672  
Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp  
210 215 220

agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg acc gtc 720  
Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val  
225 230 235 240

cta ggt 726  
Leu Gly

<210> 161  
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<220>  
<221> CDS  
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<223> Polynucleotide encoding GMBC632 scFv protein

<400> 161

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Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
1 5 10 15

tcc ctt aga ctc tcc tgt gca ggc tct ggt ttc aaa ttc agt gac gcc 96  
Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Lys Phe Ser Asp Ala  
20 25 30

tgg atg aat tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gag tac gct gca 192  
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Glu Tyr Ala Ala  
50 55 60

ccc gtg aaa gac aga ttc atc atc tca cga gat gat tca aaa gac acg 240  
Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asp Thr  
65 70 75 80

ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
85 90 95

tat tgt acg tgg gac tgg gat ttc tac tac gat atg aac gtc tgg ggc 336  
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Asp Met Asn Val Trp Gly  
100 105 110

cag ggg aca atg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga 384

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
115 120 125

ggt ggc agc ggc ggt ggc gga tcg tct gag ctg act cag gac cct gct 432  
Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
130 135 140

gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac 480  
Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
145 150 155 160

agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga cag 528  
Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
165 170 175

gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc 576  
Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
180 185 190

cca gac cga ttc ttt ggc tcc agc tca gga aac aca gct tcc ttg acc 624  
Pro Asp Arg Phe Phe Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
195 200 205

atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc 672  
Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
210 215 220

cgg gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg 720  
Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
225 230 235 240

acc gtc cta ggt 732  
Thr Val Leu Gly

<210> 162  
<211> 741  
<212> DNA  
<213> Artificial sequence

<220>  
<221> CDS  
<222> (1)..(741)  
<223> Polynucleotide encoding GMBC634 scFv protein

<400> 162

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Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
1 5 10 15

tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
20 25 30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gct gca 192

Gly	Arg	Ile	Lys	Ser	Lys	Gly	Ser	Gly	Gly	Thr	Ile	Asp	Tyr	Ala	Ala		
50						55					60						
ccc	gtg	aaa	gac	aga	ttc	acc	atc	tca	cga	gat	gat	tca	aaa	aac	acg	240	
Pro	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr		
65					70					75					80		
ctg	tat	ctg	caa	atg	aac	agt	ctg	aaa	acc	gag	gac	aca	gcc	ctg	tat	288	
Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Leu	Tyr		
				85					90					95			
tac	tgt	acg	tgg	gac	tgg	gat	ttc	tac	tac	ggg	atg	aac	gtc	tgg	ggc	336	
Tyr	Cys	Thr	Trp	Asp	Trp	Asp	Phe	Tyr	Tyr	Gly	Met	Asn	Val	Trp	Gly		
			100					105					110				
caa	ggc	acc	ctg	gtc	acc	gtc	tgc	agt	ggg	gga	ggc	ggg	tca	ggc	gga	384	
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly		
		115					120					125					
ggg	ggc	agc	ggc	ggg	ggc	gga	tgc	cag	tct	gtg	ctg	act	cag	cct	gcc	432	
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ser	Val	Leu	Thr	Gln	Pro	Ala		
		130				135					140						
tcc	gtg	tct	ggg	tct	cct	gga	cag	tgc	atc	acc	atc	tcc	tgc	act	gga	480	
Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln	Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly		
					150					155					160		
acc	agc	agt	gac	gtt	ggg	ggg	tat	aac	tat	gtc	tcc	tgg	tac	caa	caa	528	
Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr	Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln		
				165					170					175			
cac	cca	ggc	aaa	gcc	ccc	aaa	ctc	atg	att	tat	gag	ggc	agt	aag	cgg	576	
His	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Met	Ile	Tyr	Glu	Gly	Ser	Lys	Arg		
			180				185						190				
ccc	tca	ggg	gtt	tct	aat	cgc	ttc	tct	ggc	tcc	aag	tct	ggc	aac	acg	624	
Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe	Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr		
		195				200						205					
gcc	tcc	ctg	aca	atc	tct	ggg	ctc	cag	gct	gag	gac	gag	gct	gat	tat	672	
Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr		
		210				215					220						
tac	tgc	agc	tca	tat	aca	acc	agg	agc	act	cga	gtt	ttc	ggc	gga	ggg	720	
Tyr	Cys	Ser	Ser	Tyr	Thr	Thr	Arg	Ser	Thr	Arg	Val	Phe	Gly	Gly	Gly		
					230					235					240		
acc	aag	ctg	acc	gtc	cta	ggg										741	
Thr	Lys	Leu	Thr	Val	Leu	Gly											
				245													
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<212>	DNA																
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<222>	(1)..(732)																
<223>	Polynucleotide encoding GMBC635 scFv protein																

&lt;400&gt; 163

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1 5 10 15	
tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala	
20 25 30	
tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca	192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga tac acc atc tca cga gat gat tca aaa aac acg	240
Pro Val Lys Asp Arg Tyr Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
aag ggg aca atg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga	384
Lys Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly	
115 120 125	
ggt ggc agc ggc ggt ggc gga tcg tct gag ctg act cag gac cct gct	432
Gly Gly Ser Gly Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala	
130 135 140	
gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac	480
Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp	
145 150 155 160	
agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga cag	528
Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln	
165 170 175	
gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc	576
Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile	
180 185 190	
cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc	624
Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr	
195 200 205	
atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc	672
Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser	
210 215 220	
cgg gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg	720

Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240

acc gtc cta ggt 732  
 Thr Val Leu Gly

<210> 164  
 <211> 741  
 <212> DNA  
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<220>  
 <221> CDS  
 <222> (1)..(741)  
 <223> Polynucleotide encoding GMBC638 scFv protein

<400> 164

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 1 5 10 15

tca ctg aga ctc tcc tgt gaa gcc tct gga ttc gaa ttt aat tat gcc 96  
 Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Glu Phe Asn Tyr Ala  
 20 25 30

tgg atg agt tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtt 144  
 Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

ggc cgt agt aga agc gta gct agt ggt ggg aca aca gac tac gct gcg 192  
 Gly Arg Ser Arg Ser Val Ala Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

ccc ctg caa gac aga ttc acc atc tca aga gat gat tca aaa aac aca 240  
 Pro Leu Gln Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

ctg tat cta caa gtc aac agc ctg aaa atc gag gac aca ggc gtg tat 288  
 Leu Tyr Leu Gln Val Asn Ser Leu Lys Ile Glu Asp Thr Gly Val Tyr  
 85 90 95

ttc tgt aag tgg gag aaa tca gag tac tac ggt atg gac gtc tgg ggc 336  
 Phe Cys Lys Trp Glu Lys Ser Glu Tyr Tyr Gly Met Asp Val Trp Gly  
 100 105 110

cga ggg aca atg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga 384  
 Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

ggg ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga 480  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

.acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
 245  
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 <211> 759  
 <212> DNA  
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 <222> (1)..(759)  
 <223> Polynucleotide encoding GMBC639 scFv protein  
 <400> 165  
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 Gly Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Thr Pro Gly Ala  
 1 5 10 15  
 tca gtg aag gtt tcc tgc aag gca tct gga tac act ttc acc aac cac 96  
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn His  
 20 25 30  
 tat atg cac tgg gtg cga cag gcc cct gga caa gga att gag tgg gtg 144  
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Ile Glu Trp Val  
 35 40 45  
 gga gta atc aat cct agt ggt gat ggt tca agc tac gca cag acg ttc 192  
 Gly Val Ile Asn Pro Ser Gly Asp Gly Ser Ser Tyr Ala Gln Thr Phe  
 50 55 60  
 cag ggc aga gtc acc atg acc agg gac acg tcc acg agc aca gtt tac 240  
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
 65 70 75 80  
 atg gag ttg agg agc ctg aga tct gac gac acg gcc gtc tac tac tgt 288  
 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aga gat ctg ttt tac gat ttt tgg agt gat tat tat cga aat gat 336



Ala Arg Asp Leu Phe Tyr Asp Phe Trp Ser Asp Tyr Tyr Arg Asn Asp	
100 105 110	
cag tac tac tac atg gac gtc tgg ggc aag ggc acc ctg gtc acc gtc	384
Gln Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Leu Val Thr Val	
115 120 125	
tct tca ggt gga ggc ggt tca ggc gga ggt ggc agc ggc ggt ggc gga	432
Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly	
130 135 140	
tcg tct gag ctg act cag gac cct gct gtg tct gtg gcc ttg gga cag	480
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln	
145 150 155 160	
gca gtc agg atc aca tgc caa gga gac agc ctc aga agc tat tat gca	528
Ala Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala	
165 170 175	
agc tgg tac cag cag aag cca gga cag gcc cct gta ctt gtc atc tat	576
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr	
180 185 190	
ggt aaa aac aac cgg ccc tca ggg atc cca gac cga ttc tct ggc tcc	624
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser	
195 200 205	
agc tca gga aac aca gct tcc ttg acc atc act ggg gct cag gcg gaa	672
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu	
210 215 220	
gat gag gct gac tat tac tgt aac tcc cgg gac agc agt ggt aac cat	720
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His	
225 230 235 240	
gtg gta ttc ggc gga ggg acc aag ctg acc gtc cta ggt	759
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly	
245 250	
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<222> (1)..(729)	
<223> Polynucleotide encoding GMBC641 scFv protein	
<400> 166	
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1 5 10 15	
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc agc ttc agt agc tat	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Tyr	
20 25 30	
ggc atg cac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
tca gct att agt ggt agt ggt ggt agc aca tac tac gca gac tcc gtg	192
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val	
50 55 60	
aag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat	240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	
65 70 75 80	
ctg caa atg aac agt ctg aga gcc gag gac acg gct gtg tat ttc tgt	288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys	
85 90 95	
gca aag ggt gga gac cgg agc ttc cgt gct ttt gat ttc tgg ggc cag	336
Ala Lys Gly Gly Asp Arg Ser Phe Arg Ala Phe Asp Phe Trp Gly Gln	
100 105 110	
ggg aca atg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga ggt	384
Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly	
115 120 125	
ggc agc ggc ggt ggc gga tcg tct gag ctg act cag gac cct gct gtg	432
Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val	
130 135 140	
tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac agc	480
Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser	
145 150 155 160	
ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga cag gcc	528
Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala	
165 170 175	
cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc cca	576
Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro	
180 185 190	
gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc atc	624
Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile	
195 200 205	
act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc cgg	672
Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg	
210 215 220	
gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg acc	720
Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr	
225 230 235 240	
gtc cta ggt	729
Val Leu Gly	

&lt;210&gt; 167

&lt;211&gt; 729

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(729)

&lt;223&gt; Polynucleotide encoding GMBC642 scFv protein

&lt;400&gt; 167

cag gta cag ctg cag cag tca ggg gct gag gtg aag aag cct ggg gcc	48
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala	
1 5 10 15	
tca gtg aag gtt tcc tgc aag gca tct gga tac acc ttc acc atc cac	96
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ile His	
20 25 30	
tat atg cat tgg gtg cga cag gcc cct gga caa gga ctt gag tgg atg	144
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	
35 40 45	
gga ata atc aac cct ggt gat ggt agc act agt tac gca cag aac ttc	192
Gly Ile Ile Asn Pro Gly Asp Gly Ser Thr Ser Tyr Ala Gln Asn Phe	
50 55 60	
cag ggc aga gtc acc atg acc agg gac acg tcc acg agc aca gtc tat	240
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr	
65 70 75 80	
atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt	288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aga gca ggg cga act gtg act tct cac ttt gac tac tgg ggc cga	336
Ala Arg Ala Gly Arg Thr Val Thr Ser His Phe Asp Tyr Trp Gly Arg	
100 105 110	
ggc acc ctg gcc acc gtc tcc tca ggt gga ggc ggt tca ggc gga ggt	384
Gly Thr Leu Ala Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly	
115 120 125	
ggc agc ggc ggt ggc gga tgc tct gag ctg act cag gac cct gct gtg	432
Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val	
130 135 140	
tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac agc	480
Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser	
145 150 155 160	
ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga cag gcc	528
Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala	
165 170 175	
cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc cca	576
Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro	
180 185 190	
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Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile	
195 200 205	
act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc cgg	672

Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg  
 210 215 220  
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 Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Lys Phe Ser Asp Ala  
 20 25 30  
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 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gag tac gct gca 192  
 Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Glu Tyr Ala Ala  
 50 55 60  
 ccc gtg aaa gac aga ttc atc atc tca cga gat gat tca aaa gac acg 240  
 Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asp Thr  
 65 70 75 80  
 ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 tat tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 agg gga acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga 384  
 Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140  
 tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga 480

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
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 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
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 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr  
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 tat atc cac tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg 144  
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45  
 gga ata atc aac cct agt ggt ggt acc aca agc tac gca cag aag ttc 192  
 Gly Ile Ile Asn Pro Ser Gly Gly Thr Thr Ser Tyr Ala Gln Lys Phe  
 50 55 60  
 cag ggc aga gtc acc atg acc agg gac acg tcc acg agc aca gtc tac 240  
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
 65 70 75 80  
 atg gag ctg agc agc ctg aga tct gag gac acg gcc atg tat tac tgt 288

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Ala	Arg	Glu	Arg	Phe	Leu	Arg	Gly	Met	Asp	Val	Trp	Gly	Arg	Gly	Thr		
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Met	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser		
			115				120					125					
ggc	ggt	ggc	gga	tcg	gac	atc	gtg	atg	acc	cag	tct	cct	tcc	acc	ctg	432	
Gly	Gly	Gly	Gly	Ser	Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Ser	Thr	Leu		
			130			135					140						
tct	gca	tct	gta	gga	gac	aga	gtc	acc	atc	act	tgc	cgg	gcc	agt	cag	480	
Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln		
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ggc	att	agt	agc	tgg	ttg	gcc	tgg	tat	cag	cag	aaa	cca	ggg	aga	gcc	528	
Gly	Ile	Ser	Ser	Trp	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Arg	Ala		
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cct	aag	gtc	ttg	atc	tat	aag	gca	tct	act	tta	gaa	agt	ggg	gtc	cca	576	
Pro	Lys	Val	Leu	Ile	Tyr	Lys	Ala	Ser	Thr	Leu	Glu	Ser	Gly	Val	Pro		
			180					185					190				
tca	agg	ttc	agc	ggc	agt	gga	tct	ggg	aca	gat	ttc	act	ctc	acc	atc	624	
Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile		
			195				200					205					
agc	agt	ctg	caa	cct	gaa	gat	ttt	gca	act	tac	tac	tgt	caa	cag	agt	672	
Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser		
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tac	agt	acc	ccg	tgg	acg	ttc	ggc	caa	ggg	acc	aag	ctg	gag	atc	aaa	720	
Tyr	Ser	Thr	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys		
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala	
20 25 30	
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35 40 45	
ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca	192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggg	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
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Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
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Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala	
130 135 140	
tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga	480
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
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Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg	576
His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg	
180 185 190	
ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg	624
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr	
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gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat	672
Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr	
210 215 220	
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Tyr Cys Ser Ser Tyr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly	
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Thr Lys Leu Thr Val Leu Gly	
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<400> 171

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala	
20 25 30	
tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt att aaa agc aaa cgt agt ggt ggg aca ata gac tac gcc gca	192
Gly Arg Ile Lys Ser Lys Arg Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ttg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
caa ggg aca atg gtc acc gtc tct tct ggt gga ggc ggt tca ggc gga	384
Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly	
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Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Thr	
130 135 140	
gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac	480
Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp	
145 150 155 160	
agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga cag	528
Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Tyr Gln Gln Lys Pro Gly Gln	
165 170 175	
gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc	576
Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile	
180 185 190	
cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc	624



Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
195 200 205

atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc 672  
Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
210 215 220

cgg gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg 720  
Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
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Thr Val Leu Gly

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tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
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20 25 30

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Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca 192  
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
50 55 60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
65 70 75 80

ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
85 90 95

tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336  
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
100 105 110

cga gga acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga 384  
Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
115 120 125

ggc ggc agc ggc ggt ggc gga tca cag tct gtg ctg act cag cct gcc 432

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
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 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 acc agc agt gac gtt ggt ggc tat aac tat gtc tcc tgg tac caa caa 528  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
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 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
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 Thr Lys Leu Thr Val Leu Gly  
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 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30  
 tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgt att aaa agt aaa ggt agt ggt ggg aca ata gac tac gcc gca 192  
 Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60  
 ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240



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Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Ala		
			20					25					30				
tgg	atg	aac	tgg	gtc	cga	cag	gct	cca	ggg	aag	ggg	ctg	gag	tgg	gtc		144
Trp	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
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ggc	cgt	att	aaa	agt	aaa	ggg	agt	ggg	ggg	aca	aca	gac	tac	gct	gca		192
Gly	Arg	Ile	Lys	Ser	Lys	Gly	Ser	Gly	Gly	Thr	Thr	Asp	Tyr	Ala	Ala		
	50					55					60						
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Pro	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Glu	Asn	Thr		
65					70				75						80		
ctg	tat	ctg	caa	atg	aac	agc	ctg	aaa	acc	gag	gac	aca	gcc	gta	tat		288
Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr		
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tac	tgt	acg	tgg	gac	cac	agt	tac	tac	tac	gat	atg	gcc	gtc	tgg	ggc		336
Tyr	Cys	Thr	Trp	Asp	His	Ser	Tyr	Tyr	Tyr	Asp	Met	Ala	Val	Trp	Gly		
			100					105					110				
cga	ggg	acg	atg	gtc	acc	gcc	tcc	tca	ggg	gga	ggc	ggg	tca	ggc	gga		384
Arg	Gly	Thr	Met	Val	Thr	Ala	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly		
			115				120						125				
ggg	ggc	agc	ggc	ggg	ggc	gga	tcg	cag	tct	gtg	ctg	act	cag	cct	gcc		432
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ser	Val	Leu	Thr	Gln	Pro	Ala		
			130				135					140					
tcc	gtg	tct	ggg	tct	cct	gga	cag	tcg	atc	acc	atc	tcc	tgc	act	gga		480
Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln	Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly		
145					150					155					160		
acc	agc	agt	gat	gtt	ggg	ggg	tat	aac	tat	gtc	tcc	tgg	tac	caa	cag		528
Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr	Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln		
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cac	cca	ggc	aaa	gcc	ccc	aaa	ttc	atg	att	tat	gat	gtc	agt	aag	cgg		576
His	Pro	Gly	Lys	Ala	Pro	Lys	Phe	Met	Ile	Tyr	Asp	Val	Ser	Lys	Arg		
			180					185					190				
ccc	tca	ggg	ggt	tct	aat	cgc	ttc	tct	ggc	tcc	aag	tct	ggc	aac	acg		624
Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe	Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr		
			195				200					205					
gcg	tcc	ctg	acc	atc	tct	ggg	gtc	cag	gcc	gag	gac	gag	gct	gat	tat		672
Ala	Ser	Leu	Thr	Ile	Ser	Gly	Val	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr		
			210				215					220					
tac	tgc	agc	tca	tat	aca	agc	gcc	agc	act	gtg	ata	ttc	ggc	gga	ggg		720
Tyr	Cys	Ser	Ser	Tyr	Thr	Ser	Ala	Ser	Thr	Val	Ile	Phe	Gly	Gly	Gly		
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acc	aag	ctg	acc	gtc	cta	ggg											741

Thr Lys Leu Thr Val Leu Gly  
245

<210> 175

<211> 738

<212> DNA

<213> Artificial sequence

<220>

<221> CDS

<222> (1)..(738)

<223> Polynucleotide encoding GMBC653 scFv protein

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tca gtg aag gtc tcc tgc aag gct tct gga tac acc ttc acc ggc tac	96
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr	
20 25 30	
tat atg cac tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg	144
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	
35 40 45	
gga tgg atc aac cct aac agt ggt ggc aca aac tat gca cag aag ttt	192
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe	
50 55 60	
cag ggc agg gtc acc atg acc agg gac acg tcc atc agc aca gcc tac	240
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr	
65 70 75 80	
atg gag ctg agc agg ctg aga tct gac gac acg gcc gtg tat tac tgt	288
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aga ggt ggt agc cgc tac tac ggt atg gac gtc tgg agc cga gga	336
Ala Arg Gly Gly Ser Arg Tyr Tyr Gly Met Asp Val Trp Ser Arg Gly	
100 105 110	
acc ctg gtc acc gtc tct tca ggt gga ggc ggt tca ggc gga ggt ggc	384
Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly	
115 120 125	
agc ggc ggt ggc gga tcg tcc tat gtg ctg act cag ccc ccc tca gtg	432
Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu Thr Gln Pro Pro Ser Val	
130 135 140	
tct ggg acc ccc ggg cag aga gtc acc atc tct tgt tct gga ggc aga	480
Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Gly Arg	
145 150 155 160	
tcc aac atc ggc agt aat act gta aag tgg tat cag cag ctc cca gga	528
Ser Asn Ile Gly Ser Asn Thr Val Lys Trp Tyr Gln Gln Leu Pro Gly	
165 170 175	
ggc gcc ccc aaa ctc ctc atc tat ggc aat gat cag cgg ccc tca ggg	576

Ala Ala Pro Lys Leu Leu Ile Tyr Gly Asn Asp Gln Arg Pro Ser Gly  
180 185 190

gtc cct gac cga ttc tct ggc tcc aag tct ggc acc tca gcc tcc ctg 624  
Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu  
195 200 205

gcc atc act ggg gtc cag gct gaa gac gag gct gac tat tac tgc cag 672  
Ala Ile Thr Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln  
210 215 220

tca tat gac agc agc ctg agg ggt tcg agg gtc ttc gga act ggg acc 720  
Ser Tyr Asp Ser Ser Leu Arg Gly Ser Arg Val Phe Gly Thr Gly Thr  
225 230 235 240

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Lys Val Thr Val Leu Gly  
245

<210> 176  
<211> 741  
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<213> Artificial sequence

<220>  
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<223> Polynucleotide encoding GMBC654 scFv protein

<400> 176

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tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
20 25 30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

ggc cgt att aaa agc aaa cgt agt ggt ggg aca ata gac tac gcc gca 192  
Gly Arg Ile Lys Ser Lys Arg Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
50 55 60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aat acg 240  
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
65 70 75 80

ctg tat ctg caa atg aac agt ctg aaa att gag gac aca gcc ctg tat 288  
Leu Tyr Leu Gln Met Asn Ser Leu Lys Ile Glu Asp Thr Ala Leu Tyr  
85 90 95

tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336  
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
100 105 110

aaa ggg acc acg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga 384

Lys Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140  
 tcc gtg tct gga tct cct gga cag tcg atc acc atc tcc tgc act gga 480  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
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 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
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 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30  
 ggc atg agc tgg atc cgc cag gct cca ggg aag ggg cag gag tgg gtc 144  
 Gly Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Gln Glu Trp Val  
 35 40 45  
 tca gct att agt ggt agt ggt ggt agc gca tac tac gca gac tcc gtg 192

Ser Ala Ile Ser Gly Ser Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 aag ggc cgg ttc acc att tcc aga gac aat tcc aag aac acg ctg tat 240  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt 288  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 gcg aaa gcc tat agc agt gaa gac tac tgg ggc agg ggg aca atg gtc 336  
 Ala Lys Ala Tyr Ser Ser Glu Asp Tyr Trp Gly Arg Gly Thr Met Val  
 100 105 110  
 acc gtc tct tca ggt gga ggc ggt tca ggc gga ggt ggc agc ggc ggt 384  
 Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggc gga tcg aac atc cag atg acc cag tct cca tcc ttc ctg tct gca 432  
 Gly Gly Ser Asn Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala  
 130 135 140  
 tct gta gga gac aga gtc acc atc act tgc cgg gcc agt cag ggc att 480  
 Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile  
 145 150 155 160  
 aac aat tat tta gcc tgg tat cag caa aaa cca ggg aga gcc cct aag 528  
 Asn Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Lys  
 165 170 175  
 ctc ctg atc tac gct gca tcc agt tta caa agt ggg gtc cca tca agg 576  
 Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg  
 180 185 190  
 ttc agc ggc agt gga tct ggc aca gat ttc act ctc acc atc agc agc 624  
 Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser  
 195 200 205  
 ctg cag cct gat gat ttt gca act tat tac tgc caa caa tat agt aat 672  
 Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asn  
 210 215 220  
 tat ccg ctc act ttc ggc gga ggg acc aag ctg gag atc aaa cgt 717  
 Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg  
 225 230 235  
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 <211> 732  
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 <222> (1)..(732)  
 <223> Polynucleotide encoding GMBC657 scFv protein  
 <400> 178  
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tcc ctt aga ctc tcc tgt gca ggc tct ggt ttc aaa ttc agt gac gcc					96
Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Lys Phe Ser Asp Ala					
	20		25	30	
tgg atg aat tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc					144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val					
	35		40	45	
ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gag tac gct gca					192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Glu Tyr Ala Ala					
	50		55	60	
ccc gtg aaa gac aga ttc atc atc tca cga gat gat tca aaa gac acg					240
Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asp Thr					
	65		70	75	80
ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat					288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr					
	85		90	95	
tat tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc					336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly					
	100		105	110	
cag gga acc ctg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga					384
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly					
	115		120	125	
ggg ggc agc ggc ggt ggc gga tgc tct gag ctg act cag gac cct gct					432
Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala					
	130		135	140	
gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac					480
Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp					
	145		150	155	160
agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga cag					528
Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln					
	165		170	175	
gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc					576
Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile					
	180		185	190	
cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc					624
Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr					
	195		200	205	
atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc					672
Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser					
	210		215	220	
cgg gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg					720
Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu					
	225		230	235	240
acc gtc cta ggt					732

Thr Val Leu Gly

&lt;210&gt; 179

&lt;211&gt; 741

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(741)

&lt;223&gt; Polynucleotide encoding GMBC658 scFv protein

&lt;400&gt; 179

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tcc ctt aga ctt tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala	
20 25 30	
tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gct gca	192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
cgg ggg acc acg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga	384
Arg Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc	432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala	
130 135 140	
tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga	480
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa	528
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg	576

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
180 185 190

ccc tca ggg gtt tct aat cgc ttc tct ggt tcc aag tct ggc aac acg 624  
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
195 200 205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
210 215 220

tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
225 230 235 240

acc aag ctg acc gtc cta ggt 741  
Thr Lys Leu Thr Val Leu Gly  
245

<210> 180  
<211> 741  
<212> DNA  
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<220>  
<221> CDS  
<222> (1)..(741)  
<223> Polynucleotide encoding GMBC659 scFv protein

<400> 180

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tca ctg aga ctc tcc tgt gaa gcc tct gga ttc gaa ttt aat tat gcc 96  
Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Glu Phe Asn Tyr Ala  
20 25 30

tgg atg agt tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtt 144  
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

ggc cgt agt aga agc gaa gct agt ggt ggg aca aca gac tac gct gca 192  
Gly Arg Ser Arg Ser Glu Ala Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
50 55 60

ccc ctg caa gac aga ttc acc atc tca aga gat gat tca aaa aac aca 240  
Pro Leu Gln Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
65 70 75 80

ctg tat cta caa gtc aac agc ctg aaa atc gag gac aca ggc gtg tat 288  
Leu Tyr Leu Gln Val Asn Ser Leu Lys Ile Glu Asp Thr Gly Val Tyr  
85 90 95

ttc tgt aag tgg gag aaa tca gag tac tac ggt atg gac gtc tgg ggc 336  
Phe Cys Lys Trp Glu Lys Ser Glu Tyr Tyr Gly Met Asp Val Trp Gly  
100 105 110

aga ggc acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga 384

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140  
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 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
 245  
 <210> 181  
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 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
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 tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc att ttc agt gac gcc 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asp Ala  
 20 25 30  
 tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn, Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca 192

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
 Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

ctg tat ctg caa atg aac agt cta aaa acc gag gac aca gcc ctg tat 288  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110

cag ggc acc ccg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga 384  
 Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

ggt ggc agc ggc ggt ggc gga tcc cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

tcc gtg tct ggg tct cct gga cag tcc atc acc atc tcc tgc act gga 480  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175

cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190

ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

tac tgc agc tca tat aca acc agg agc act cga gtc ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
 245

<210> 182  
 <211> 729  
 <212> DNA  
 <213> Artificial sequence

<220>  
 <221> CDS  
 <222> (1)..(729)  
 <223> Polynucleotide encoding GMBC662 scFv protein

&lt;400&gt; 182

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1           5           10           15

tcg gtg aag gtc tcc tgc aag gct tct gga ggc acc ttc agc agc tat      96
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20           25           30

act atc agc tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg      144
Thr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35           40           45

gga agg atc atc cct atc ctt ggt ata gca aac tac gca cag aag ttc      192
Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50           55           60

cag ggc aga gtc acg att acc gcg gac aaa tcc acg agc aca gcc tac      240
Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65           70           75           80

atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt      288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85           90           95

gcg aga gaa aag ttg agg gac ttc cag cac tgg ggc caa gga acc ctg      336
Ala Arg Glu Lys Leu Arg Asp Phe Gln His Trp Gly Gln Gly Thr Leu
100          105          110

gtc acc gtc tct tca ggt gga ggc ggt tca ggc gga ggt ggc agc ggc      384
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115          120          125

ggt ggc gga tcg cag tct gtg ctg act cag cct gcc tcc gtg tct ggg      432
Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser Gly
130          135          140

tct cct gga cag tcg atc acc atc tcc tgc act gga acc agc agt gac      480
Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
145          150          155          160

gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa cac cca ggc aaa      528
Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys
165          170          175

gcc ccc aaa ctc atg att tat gag ggc agt aag cgg ccc tca ggg att      576
Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser Gly Ile
180          185          190

tct aat cgc ttc tct ggc tcc aag tct ggc aac acg gcc tcc ctg aca      624
Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
195          200          205

atc tct agg ctc cag gct gag gac gag gct gat tat tac tgc agc tca      672
Ile Ser Arg Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
210          215          220

tat aca acc agg agc act cga gtt ttc ggc gga ggg acc aag ctg acc      720

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Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Thr  
 225 230 235 240

gtc cta ggt  
 Val Leu Gly

729

<210> 183  
 <211> 741  
 <212> DNA  
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<220>  
 <221> CDS  
 <222> (1)..(741)  
 <223> Polynucleotide encoding GMBC664 scFv protein

<400> 183

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 Glu Val Gln Leu Val Glu Thr Gly Gly Ala Leu Val Lys Pro Gly Gly  
 1 5 10 15

tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gct gca 192  
 Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
 Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95

tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg agc 336  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Ser  
 100 105 110

cgg ggg aca atg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga 384  
 Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125

ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140

tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga 480  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160

acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
165 170 175

cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
180 185 190

ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
195 200 205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
210 215 220

tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
225 230 235 240

acc aag ctg acc gtc cta ggt 741  
Thr Lys Leu Thr Val Leu Gly  
245

<210> 184  
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<222> (1)..(732)  
<223> Polynucleotide encoding GMBC665 scFv protein

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tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
20 25 30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

ggc cgt att aaa agt aaa ggt agt ggt ggg aca ata gac tac gcc gca 192  
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
50 55 60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
65 70 75 80

ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
85 90 95

tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336



Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 caa ggg aca atg gtc acc gtc tct tca ggt gga ggc ggt tca ggc gga 384  
 Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tgc tct gag ctg act cag gac cct gct 432  
 Gly Gly Ser Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140  
 gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac 480  
 Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160  
 agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga cag 528  
 Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln  
 165 170 175  
 gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc 576  
 Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile  
 180 185 190  
 cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc 624  
 Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205  
 atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc 672  
 Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser  
 210 215 220  
 cgg gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg 720  
 Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu  
 225 230 235 240  
 acc gtc cta ggt 732  
 Thr Val Leu Gly  
  
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 tca ctg aga ctc tcc tgt gaa gcc tct gga ttc gaa ttt aat tat gcc 96  
 Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Glu Phe Asn Tyr Ala  
 20 25 30  
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Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt agt aga agc gaa gct agt ggt ggg aca aca gac tac gct gca	192
Gly Arg Ser Arg Ser Glu Ala Ser Gly Gly Thr Thr Asp Tyr Ala Ala	
50 55 60	
ccc ctg caa gac aga ttc acc atc tca aga gat gat tca aaa aac aca	240
Pro Leu Gln Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat'cta caa gtc aac agc ctg aaa atc gag gac aca ggc gtg tat	288
Leu Tyr Leu Gln Val Asn Ser Leu Lys Ile Glu Asp Thr Gly Val Tyr	
85 90 95	
ttc tgt aag tgg gag aaa tca gag tac tac ggt atg gac gtc tgg ggc	336
Phe Cys Lys Trp Glu Lys Ser Glu Tyr Tyr Gly Met Asp Val Trp Gly	
100 105 110	
aaa ggg aca atg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga	384
Lys Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
ggc ggc agc ggc ggt ggc gga tcg cag tct gtg ttg acg cag ccg ccc	432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro	
130 135 140	
tca gtg tct gcg gcc cca gga cag aag gtc acc att tcc tgc tct gga	480
Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile Ser Cys Ser Gly	
145 150 155 160	
agc acc tcc aac att ggg aat aat tat gtc tcc tgg tac caa cag cac	528
Ser Thr Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp Tyr Gln Gln His	
165 170 175	
cca ggc aaa gcc ccc aaa ctc atg att tat gat gtc agt aag cgg ccc	576
Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Lys Arg Pro	
180 185 190	
tca ggc gtc cct gac cga ttc tct ggc tcc aag tct ggc aac tca gcc	624
Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Ser Ala	
195 200 205	
tcc ctg gac atc agt ggg ctc cag tct gag gat gag gct gat tat tac	672
Ser Leu Asp Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr	
210 215 220	
tgt gca gca tgg gat gac agc ctg agt gaa ttt ctc ttc gga act ggg	720
Cys Ala Ala Trp Asp Asp Ser Leu Ser Glu Phe Leu Phe Gly Thr Gly	
225 230 235 240	
acc aag ctg acc gtc cta ggt	741
Thr Lys Leu Thr Val Leu Gly	
245	
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&lt;222&gt; (1)..(741)

&lt;223&gt; Polynucleotide encoding GMBC667 scFv protein

&lt;400&gt; 186

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Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1           5           10           15

tcc ctt aga ctg tcc tgt gca ggc tct ggt ttc cct ttc agt gac gcc      96
Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Pro Phe Ser Asp Ala
20           25           30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc      144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35           40           45

ggc cgt att aaa agt aaa ggt agt ggt ggg aca ata gac tac gct gca      192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala
50           55           60

ccc gtg aaa gac aga ttc agg atc tca cga gat gat tca aaa aac acg      240
Pro Val Lys Asp Arg Phe Arg Ile Ser Arg Asp Asp Ser Lys Asn Thr
65           70           75           80

ctg tat ctg caa atg aac agt ctg aac atc gag gac aca gcc ctc tat      288
Leu Tyr Leu Gln Met Asn Ser Leu Asn Ile Glu Asp Thr Ala Leu Tyr
85           90           95

tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggg      336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly
100          105          110

cag ggg acc acg gtc acc gtc tct tca ggt gga ggc ggt tca ggc gga      384
Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
115          120          125

ggt ggc agc ggc ggt ggc gga tgc cag tct gtg ctg act cag cct gcc      432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala
130          135          140

tcc gtg tct ggg tct cct gga cag tgc atc acc atc tcc tgc act gga      480
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly
145          150          155          160

acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa      528
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln
165          170          175

cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg      576
His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg
180          185          190

ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg      624
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
195          200          205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat      672

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Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240

acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
 245

<210> 187  
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<220>  
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 <223> Polynucleotide encoding GMBC668 scFv protein

<400> 187

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tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30

tgg atg aac tgg gtc cgg cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

ggc cgt att aaa agt aaa ggt agt ggt ggg aca aca gac tac gct gca 192  
 Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Thr Asp Tyr Ala Ala  
 50 55 60

ccc gtg aaa ggc aga ttc acc atc tca aga gat gat tca gaa aac acg 240  
 Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asn Thr  
 65 70 75 80

ctg tat ctg caa atg aac agc ctg aaa acc gag gac aca gcc gta tat 288  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr  
 85 90 95

tac tgt acg tgg gac cac agt tac tac tac gat atg gcc gtc tgg ggc 336  
 Tyr Cys Thr Trp Asp His Ser Tyr Tyr Tyr Asp Met Ala Val Trp Gly  
 100 105 110

cga ggc acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga 384  
 Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125

ggt ggc agc ggc ggt ggc gga tcg tct gag ctg act cag gac cct gct 432  
 Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140

gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac 480

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Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp
145                      150                      155                      160

agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga cag      528
Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln
                      165                      170                      175

gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc      576
Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile
                      180                      185                      190

cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc      624
Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr
                      195                      200                      205

atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc      672
Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser
                      210                      215                      220

cgg gac agc agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg      720
Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu
225                      230                      235                      240

acc gtc cta ggt
Thr Val Leu Gly
732

<210> 188
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<213> Artificial sequence

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<223> Polynucleotide encoding GMBC669 scFv protein

<400> 188

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tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala
20                      25                      30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc      144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35                      40                      45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gct gca      192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala
50                      55                      60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg      240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                      70                      75                      80

ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat      288

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Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
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Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
caa ggc acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga	384
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly	
115 120 125	
ggc ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct ccc	432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro	
130 135 140	
tcc gcg tcc ggg tct cct gga cag tca gtc acc atc tcc tgc act gga	480
Ser Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly	
145 150 155 160	
acc agc agt gat gtt ggt ggt tat aac tat gtc tcc tgg tac caa cag	528
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aaa gcc ccc aaa ttc atg att tat gat gtc agt aag cgg	576
His Pro Gly Lys Ala Pro Lys Phe Met Ile Tyr Asp Val Ser Lys Arg	
180 185 190	
ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg	624
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr	
195 200 205	
gcg tcc ctg acc atc tct ggg gtc cag gct gag gac gag gct gat tat	672
Ala Ser Leu Thr Ile Ser Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr	
210 215 220	
tac tgc agc tca tat aca agc gcc agc act gtg ata ttc ggc gga ggg	720
Tyr Cys Ser Ser Tyr Thr Ser Ala Ser Thr Val Ile Phe Gly Gly Gly	
225 230 235 240	
acc aag ctg acc gtc cta ggt	741
Thr Lys Leu Thr Val Leu Gly	
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tcc ctt aga ctc tcc tgt gta gcc tct ggt ttc act ttc agt gac gcc	96

Ser	Leu	Arg	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Ala		
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Trp	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
ggc	cgt	att	aaa	agt	aaa	ggg	agt	ggg	ggg	aca	ata	gac	tac	gct	gca	192	
Gly	Arg	Ile	Lys	Ser	Lys	Gly	Ser	Gly	Gly	Thr	Ile	Asp	Tyr	Ala	Ala		
		50				55					60						
ccc	gtg	aaa	gac	aga	ttc	att	atc	tca	cga	gat	gat	tca	aaa	aac	acg	240	
Pro	Val	Lys	Asp	Arg	Phe	Ile	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr		
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ctg	tat	ctg	caa	gtg	aac	agt	ctg	aaa	acc	gag	gac	aca	gcc	cta	tat	288	
Leu	Tyr	Leu	Gln	Val	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Leu	Tyr		
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tat	tgt	acg	tgg	gac	tgg	gat	ttc	tac	tac	ggg	atg	aac	gtc	tgg	ggc	336	
Tyr	Cys	Thr	Trp	Asp	Trp	Asp	Phe	Tyr	Tyr	Gly	Met	Asn	Val	Trp	Gly		
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caa	ggc	acc	ctg	gtc	acc	gtc	tcc	tct	ggg	gga	ggc	ggg	tca	ggc	gga	384	
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly		
		115					120					125					
ggg	ggc	agc	ggc	ggg	ggc	gga	tgc	cag	tct	gtg	ctg	act	cag	cct	gcc	432	
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ser	Val	Leu	Thr	Gln	Pro	Ala		
		130				135					140						
tcc	gtg	tct	ggg	tct	cct	gga	cag	tgc	atc	acc	atc	tcc	tgc	act	gga	480	
Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln	Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly		
		145			150				155					160			
acc	agc	agt	gac	gtt	ggg	ggg	tat	aac	tat	gtc	tcc	tgg	tac	caa	caa	528	
Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr	Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln		
			165				170							175			
cac	cca	ggc	aaa	gcc	ccc	aaa	ctc	atg	att	tat	gag	ggc	agt	aag	cgg	576	
His	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Met	Ile	Tyr	Glu	Gly	Ser	Lys	Arg		
		180					185					190					
ccc	tca	ggg	gtt	tct	aat	cgc	ttc	tct	ggc	tcc	aag	tct	ggc	aac	acg	624	
Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe	Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr		
		195				200					205						
gcc	tcc	ctg	aca	atc	tct	ggg	ctc	cag	gct	gag	gac	gag	gct	gat	tat	672	
Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr		
		210				215					220						
tac	tgc	agc	tca	tat	aca	acc	agg	agc	act	cga	gtt	ttc	ggc	gga	ggg	720	
Tyr	Cys	Ser	Ser	Tyr	Thr	Thr	Arg	Ser	Thr	Arg	Val	Phe	Gly	Gly	Gly		
		225			230				235					240			
acc	aag	ctg	acc	gtc	cta	ggg										741	
Thr	Lys	Leu	Thr	Val	Leu	Gly											
				245													

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 <213> Artificial sequence

<220>  
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 <223> Polynucleotide encoding GMBC672 scFv protein

<400> 190

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1 5 10 15	
tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala	
20 25 30	
tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gct gca	192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat ctg caa atg aat agt ctg aaa acc gag gac aca gcc ctg tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
cag gga acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga	384
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly	
115 120 125	
ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc	432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala	
130 135 140	
tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga	480
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa	528
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg	576
His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg	
180 185 190	
ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg	624



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Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
    195                200                205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat      672
Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
    210                215                220

tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gaa ggg      720
Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Glu Gly
    225                230                235                240

acc aag ctg acc gtc cta ggt      741
Thr Lys Leu Thr Val Leu Gly
    245

<210> 191
<211> 729
<212> DNA
<213> Artificial sequence

<220>
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<222> (1)..(729)
<223> Polynucleotide encoding GMBC673 scFv protein

<400> 191

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
1                5                10                15

tcc ctg aga ctc tcc tgt gca gcc tct gga ttt ccc att ggc agt cac      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Pro Ile Gly Ser His
    20                25                30

tgg atg agc tgg gtc cgc cag tct ccg ggg aag ggg ctg gag tgg gtg      144
Trp Met Ser Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Val
    35                40                45

gcc agc atc aag caa gat gga cgt gag aag cac ttt gtg gac tct gtg      192
Ala Ser Ile Lys Gln Asp Gly Arg Glu Lys His Phe Val Asp Ser Val
    50                55                60

aag ggc cga ttc ggc atc tcc aga gac aac gcc aag gac tca ctg tat      240
Lys Gly Arg Phe Gly Ile Ser Arg Asp Asn Ala Lys Asp Ser Leu Tyr
    65                70                75                80

ctc caa atg aac agc ctg aga atc gag gac acg gct gtc tac tac tgt      288
Leu Gln Met Asn Ser Leu Arg Ile Glu Asp Thr Ala Val Tyr Tyr Cys
    85                90                95

gcg aga gag acg tac ggg gga tac tac tat tac ttc atg gac gtc tgg      336
Ala Arg Glu Thr Tyr Gly Gly Tyr Tyr Tyr Phe Met Asp Val Trp
    100                105                110

ggc cga ggc acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc      384
Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    115                120                125

gga ggt ggc agc ggc ggt ggc gga tcg tct gag ctg act cag gac cct      432

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Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro  
 130 135 140  
 gct gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc caa gga 480  
 Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly  
 145 150 155 160  
 gac agc ctc aga agc tat tat gca agc tgg tac cag cag aag cca gga 528  
 Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly  
 165 170 175  
 cag gcc cct gta ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg 576  
 Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly  
 180 185 190  
 atc cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg 624  
 Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu  
 195 200 205  
 acc atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt cag 672  
 Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln  
 210 215 220  
 acc tgg ggc cct ggc att cga gtg ttc ggc gga ggg acc aag ctg acc 720  
 Thr Trp Gly Pro Gly Ile Arg Val Phe Gly Gly Gly Thr Lys Leu Thr  
 225 230 235 240  
 gtc cta ggt 729  
 Val Leu Gly  
  
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 1 5 10 15  
 tcc ctg aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt cac gcc 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Ala  
 20 25 30  
 tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgt att aaa agc aaa gct agt ggt ggg aca ata gac tac gcc gca 192  
 Gly Arg Ile Lys Ser Lys Ala Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60  
 ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240

Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80  
 ctg tat ctg cac atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
 Leu Tyr Leu His Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggg 336  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 cgg ggg aca atg gtc acc gtc tct tca ggt gga ggc ggt tca ggc gga 384  
 Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tgc cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140  
 tcc gtg tct ggg tct cct gga cag ccg atc acc atc tcc tgc act gga 480  
 Ser Val Ser Gly Ser Pro Gly Gln Pro Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
 245  
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 <212> DNA  
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 <222> (1)..(741)  
 <223> Polynucleotide encoding GMBC678 scFv protein  
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Glu 1	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Lys	Pro	Gly	Gly	
				5					10					15		
tcc	ctt	aga	ctc	tcc	tgt	gca	gcc	tct	ggc	ttc	act	ttc	agt	gac	gcc	96
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Ala	
			20					25					30			
tgg	atg	aac	tgg	gtc	cgc	cag	gct	cca	ggg	aag	ggg	ctg	gag	tgg	gtc	144
Trp	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
		35					40					45				
ggc	cgt	att	aaa	agt	aaa	ggc	agt	ggc	ggg	aca	ata	gac	tac	gcc	gca	192
Gly	Arg	Ile	Lys	Ser	Lys	Gly	Ser	Gly	Gly	Thr	Ile	Asp	Tyr	Ala	Ala	
	50					55				60						
ccc	gtg	aaa	gac	aga	ttc	acc	atc	tca	cga	gat	gat	tca	aaa	aac	acg	240
Pro	Val	Lys	Asp	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Thr	
65					70					75					80	
ctg	tat	ctg	caa	atg	aac	agt	ctg	aaa	acc	gag	gac	aca	gcc	ctg	tat	288
Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Leu	Tyr	
			85						90					95		
tac	tgt	acg	tgg	gac	tgg	gat	ttc	tac	tac	ggc	atg	aac	gtc	tgg	ggc	336
Tyr	Cys	Thr	Trp	Asp	Trp	Asp	Phe	Tyr	Tyr	Gly	Met	Asn	Val	Trp	Gly	
			100				105						110			
cag	gga	acc	ctg	gtc	acc	gtc	tcc	tca	ggc	ggg	ggc	ggc	tca	ggc	gga	384
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	
		115					120					125				
ggc	ggc	agc	ggc	ggc	ggc	gga	tcg	cag	tct	gtg	ctg	act	cag	cct	ccc	432
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Ser	Val	Leu	Thr	Gln	Pro	Pro	
		130				135					140					
tcc	gcg	tcc	ggg	tct	cct	gga	cag	tca	gtc	acc	atc	tcc	tgc	act	gga	480
Ser	Ala	Ser	Gly	Ser	Pro	Gly	Gln	Ser	Val	Thr	Ile	Ser	Cys	Thr	Gly	
145					150					155					160	
acc	agc	agt	gat	ggt	ggc	ggc	tat	aac	tat	gtc	tcc	tgg	tac	caa	cag	528
Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr	Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln	
				165					170					175		
cac	cca	ggc	aaa	gcc	ccc	aaa	ttc	atg	att	tat	gat	gtc	agt	aag	cgg	576
His	Pro	Gly	Lys	Ala	Pro	Lys	Phe	Met	Ile	Tyr	Asp	Val	Ser	Lys	Arg	
			180					185					190			
ccc	tca	ggg	ggt	tct	aat	cgc	ttc	tct	ggc	tcc	aag	tct	ggc	aac	acg	624
Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe	Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr	
		195					200					205				
gcg	tcc	ctg	acc	atc	tct	ggg	gtc	cag	gct	gag	gac	gag	gct	gat	tat	672
Ala	Ser	Leu	Thr													

Thr Lys Leu Thr Val Leu Gly  
245

<210> 194

<211> 741

<212> DNA

<213> Artificial sequence

<220>

<221> CDS

<222> (1) .. (741)

<223> Polynucleotide encoding GMBC679 scFv protein

<400> 194

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly	
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tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala	
20 25 30	
tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt att aaa agt aaa ggt agt ggt ggg aca aca gac tac gct gca	192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Thr Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga ttc acc atc tca aga gat gat tca gaa aac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asn Thr	
65 70 75 80	
ctg tat cta caa atg aac agc ctg aaa acc gag gac aca gcc gta tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr	
85 90 95	
tac tgt acg tgg gac cat agt tat tat tat gat atg gcc gtc tgg ggc	336
Tyr Cys Thr Trp Asp His Ser Tyr Tyr Tyr Asp Met Ala Val Trp Gly	
100 105 110	
cga ggc acc ctg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga	384
Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc	432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala	
130 135 140	
tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga	480
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa	528
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aaa gcc ccc aaa ctc gtg att tat gag ggc agt aag cgg	576

His Pro Gly Lys Ala Pro Lys Leu Val Ile Tyr Glu Gly Ser Lys Arg  
180 185 190

ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
195 200 205

gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
210 215 220

tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
225 230 235 240

acc aag ctg acc gtc cta ggt 741  
Thr Lys Leu Thr Val Leu Gly  
245

<210> 195  
<211> 720  
<212> DNA  
<213> Artificial sequence

<220>  
<221> CDS  
<222> (1)..(720)  
<223> Polynucleotide encoding GMBC681 scFv protein

<400> 195

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Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Gly  
1 5 10 15

tcc ctg aga ctc tcc tgt gca gcg tct gga ttc acc ttc agt agc tat 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
20 25 30

ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg 144  
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

gca ttt ata cgg tat gat gga agt aat aaa tac tat gca gac tcc gtg 192  
Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
50 55 60

aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240  
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
65 70 75 80

ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt 288  
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

gcg aaa gga gga act ggc tac ttc gat ctc tgg ggc cga gga acc ctg 336  
Ala Lys Gly Gly Thr Gly Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu  
100 105 110

gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga ggt ggc agc ggc 384

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Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115                      120                      125

ggt ggc gga tcg gac atc cag atg acc cag tct cct tcc acc ctg tct      432
Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser
130                      135                      140

gca tct att gga gac aga gtc acc atc acc tgc cgg gcc agt gag ggt      480
Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly
145                      150                      155                      160

att tat cac tgg ttg gcc tgg tat cag cag aag cca ggg aaa gcc cct      528
Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
165                      170                      175

aaa ctc ctg atc tat aag gcc tct agt tta gcc agt ggg gcc cca tca      576
Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser
180                      185                      190

agg ttc agc ggc agt gga tct ggg aca gat ttc act ctc acc atc agc      624
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
195                      200                      205

agc ctg cag cct gat gat ttt gca act tat tac tgc caa caa tat agt      672
Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser
210                      215                      220

aat tat ccg ctc act ttc ggc gga ggg acc aag ctg gag atc aaa cgt      720
Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
225                      230                      235                      240

<210> 196
<211> 732
<212> DNA
<213> Artificial sequence

<220>
<221> CDS
<222> (1)..(732)
<223> Polynucleotide encoding GMBC682 scFv protein

<400> 196

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Lys Pro Gly Gly
1      5      10      15

tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc aaa ttc agt gac gcc      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Asp Ala
20      25      30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc      144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35      40      45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gct gca      192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala
50      55      60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg      240

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-204-



Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Arg	
1 5 10 15	
tcc ctg aga ctc tcc tgt gca gcg tct gga ttc acc ttc agt agc tat	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr	
20 25 30	
ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg	144
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
gca gtt ata tca tat gat gga agt aat aaa tac tat gca gac tcc gtg	192
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val	
50 55 60	
aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat	240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	
65 70 75 80	
ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt	288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aaa cgg gca gca gct ggt acc ctt gac tac tgg ggg cag ggg acc	336
Ala Lys Arg Ala Ala Ala Gly Thr Leu Asp Tyr Trp Gly Gln Gly Thr	
100 105 110	
acg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga ggt ggc agc	384
Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Ser	
115 120 125	
ggc ggt ggc gga tcg tct gag ctg act cag gac cct gct gtg tct gtg	432
Gly Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val	
130 135 140	
gcc ttg gga cag aca gtc agg atc aca tgc caa gga gac agt ctc aga	480
Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg	
145 150 155 160	
agc tat tat gca agc tgg tac cag cag aag cca gga cag gcc cct gta	528
Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val	
165 170 175	
ctt gtc atc tat ggt aaa aac aac cgg ccc tca ggg atc cca gac cga	576
Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg	
180 185 190	
ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc atc act ggg	624
Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly	
195 200 205	
gct cag gcg gaa gat gag gct gac tat tac tgt aac tcc cgg gac agc	672
Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser	
210 215 220	
agt ggt aac cat gtg gta ttc ggc gga ggg acc aag ctg acc gtc cta	720
Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu	
225 230 235 240	
ggt	723

Gly

<210> 198  
 <211> 741  
 <212> DNA  
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<220>  
 <221> CDS  
 <222> (1)..(741)  
 <223> Polynucleotide encoding GMBC684 scFv protein

<400> 198

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Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly	
1 5 10 15	
tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc aaa ttc agt gac gcc	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Asp Ala	
20 25 30	
tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt att aaa agc aaa ggt agt ggc ggg aca ata gac tac gct gca	192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc cta tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
caa gga acc ccg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga	384
Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
ggg ggc agc ggc ggt ggc gga tcg cag tct gcg ctg act cag cct gcc	432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala	
130 135 140	
tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga	480
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa	528
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg	576

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
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 Thr Lys Leu Thr Val Leu Gly  
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 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
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 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca 192  
 Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60  
 ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
 Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80  
 ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 aag ggg aca atg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga 384

Lys Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tgc tct gag ctg act cag gac cct gct 432  
 Gly Gly Ser Gly Gly Gly Ser Ser Glu Leu Thr Gln Asp Pro Ala  
 130 135 140  
 gtg tct gtg gcc ttg gga cag aca gtc agg atc act tgc caa gga gac 480  
 Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp  
 145 150 155 160  
 agt ctc aga agc tat tac aca aac tgg ttc cag cag aag cca gga cag 528  
 Ser Leu Arg Ser Tyr Tyr Thr Asn Trp Phe Gln Gln Lys Pro Gly Gln  
 165 170 175  
 gcc cct cta ctt gtc gtc tat gct aaa aat aag cgg ccc tca ggg atc 576  
 Ala Pro Leu Leu Val Val Tyr Ala Lys Asn Lys Arg Pro Ser Gly Ile  
 180 185 190  
 cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg acc 624  
 Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr  
 195 200 205  
 atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt cat tcc 672  
 Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys His Ser  
 210 215 220  
 cgg gac agc agt ggt aac cat gtg ctt ttc ggc gga ggg acc aag ctg 720  
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 225 230 235 240  
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 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30  
 tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca 192

Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60  
 ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
 Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80  
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 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 cag ggg acc acg gtc acc gtc tcc tca ggt gga ggc ggt tca ggc gga 384  
 Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tgc cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140  
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 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa 528  
 Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
 245

&lt;210&gt; 201

&lt;211&gt; 741

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(741)

&lt;223&gt; Polynucleotide encoding GMBC687 scFv protein

&lt;400&gt; 201

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tcg gtg aaa gtc tcc tgc aag gct cct gga gac acc ttc agc aac tat Ser Val Lys Val Ser Cys Lys Ala Pro Gly Asp Thr Phe Ser Asn Tyr 20 25 30	96
att ttc aac tgg gtg cga cag gcc cct gga caa gga ctt gag tgg atg Ile Phe Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45	144
gga ggg atc atc cca aag ttt ggt aca gta aat gat gca cac aag ttc Gly Gly Ile Ile Pro Lys Phe Gly Thr Val Asn Asp Ala His Lys Phe 50 55 60	192
caa gac aga gtc acc att gcc gct gac gaa tcc acg aac acg gcc tcc Gln Asp Arg Val Thr Ile Ala Ala Asp Glu Ser Thr Asn Thr Ala Ser 65 70 75 80	240
atg gag ctg agc agc ctg aca tct gag gac acg gcc gtt tat tac tgt Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95	288
gcg tgc gaa ccc att ccc aag gac tac ggt gac gtt aat ggt ctt gaa Ala Cys Glu Pro Ile Pro Lys Asp Tyr Gly Asp Val Asn Gly Leu Glu 100 105 110	336
atc tgg ggc aaa ggg aca atg gtc acc gtc tct tca ggt gga ggc ggt Ile Trp Gly Lys Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly 115 120 125	384
tca ggc gga ggt ggc agc ggc ggt ggc gga tgc gac atc cag atg acc Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr 130 135 140	432
cag tct cct tcc acc ctg tct gca tct att gga gac aga gtc acc atc Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile 145 150 155 160	480
acc tgc cgg gcc agt gag ggt att tat cac tgg ttg gcc tgg tat cag Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln 165 170 175	528
cag aag cca ggg aaa gcc cct aaa ctc ctg atc tat aag gcc tct agt Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser 180 185 190	576
tta gcc agt ggg gcc cca tca agg ttc agc ggc agt gga tct ggg aca Leu Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr 195 200 205	624
gat ttc act ctc acc atc agc agc ctg cag cct gat gat ttt gca act Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr 210 215 220	672
tat tac tgc caa caa tat agt aat tat ccg ctc act ttc ggc gga ggg	720

Tyr Tyr Cys Gln Gln Tyr Ser Asn Tyr Pro Leu Thr Phe Gly Gly Gly  
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 tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
 20 25 30  
 tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca 192  
 Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
 50 55 60  
 ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
 Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80  
 ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
 Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
 85 90 95  
 tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336  
 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 cag gga acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga 384  
 Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct ccc 432  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro  
 130 135 140  
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 Ser Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 acc agc agt gat gtt ggt ggt tat aac tat gtc tcc tgg tac caa cag 528

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln  
165 170 175

cac cca ggc aaa gcc ccc aaa ttc atg att tat gat gtc agt aag cgg 576  
His Pro Gly Lys Ala Pro Lys Phe Met Ile Tyr Asp Val Ser Lys Arg  
180 185 190

ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
195 200 205

gcg tcc ctg acc atc tct ggg gtc cag gct gag gac gag gct gat tat 672  
Ala Ser Leu Thr Ile Ser Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr  
210 215 220

tac tgc agc tca tat aca agc gcc agc act gtg gta ttc ggc gga ggg 720  
Tyr Cys Ser Ser Tyr Thr Ser Ala Ser Thr Val Val Phe Gly Gly Gly  
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Thr Lys Leu Thr Val Leu Gly  
245

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<400> 203

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tcc ctg aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala  
20 25 30

tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca 192  
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
50 55 60

ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
65 70 75 80

ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat 288  
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr  
85 90 95

tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc 336



Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
 100 105 110  
 aga ggc acc ctg gtc act gtc tct tca ggc gga ggc ggt tca ggc gga 384  
 Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly  
 115 120 125  
 ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc 432  
 Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala  
 130 135 140  
 tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga 480  
 Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly  
 145 150 155 160  
 acc agc agt gac gtt ggt ggt tat atc tat gtc tcc tgg tac caa caa 528  
 Thr Ser Ser Asp Val Gly Gly Tyr Ile Tyr Val Ser Trp Tyr Gln Gln  
 165 170 175  
 cac cca ggc aga gcc ccc aaa ctc atg att tat gag ggc agt aag cgg 576  
 His Pro Gly Arg Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg  
 180 185 190  
 ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg 624  
 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr  
 195 200 205  
 gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat 672  
 Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220  
 tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg 720  
 Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly  
 225 230 235 240  
 acc aag ctg acc gtc cta ggt 741  
 Thr Lys Leu Thr Val Leu Gly  
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 1 5 10 15  
 tca atg aaa gtc tcc tgc aag act tct gga gac acc ttc aac ggc ttt 96  
 Ser Met Lys Val Ser Cys Lys Thr Ser Gly Asp Thr Phe Asn Gly Phe  
 20 25 30  
 tat gta cac tgg gtg cga cag gcc cct ggc caa ggg ctt gag tgg atg 144

Tyr	Val	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met		
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Gly	Arg	Ile	Asn	Pro	Asn	Gly	Gly	Gly	Thr	Asn	Tyr	Ala	Gln	Lys	Phe		
	50					55					60						
cag	ggc	agg	gtc	acc	atg	acc	agg	gac	acg	tcc	atg	aac	aca	gcc	tac	240	
Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Met	Asn	Thr	Ala	Tyr		
	65				70				75					80			
atg	gag	ttg	agg	agc	ctg	aga	tct	gac	gac	acg	gcc	gtc	tac	tac	tgt	288	
Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
			85					90					95				
gcg	aga	gat	ctg	ttt	tac	gat	ttt	tgg	agt	gat	tat	tat	cga	aat	gat	336	
Ala	Arg	Asp	Leu	Phe	Tyr	Asp	Phe	Trp	Ser	Asp	Tyr	Tyr	Arg	Asn	Asp		
			100					105					110				
cag	tac	tac	tac	atg	gac	gtc	tgg	ggc	cgg	ggc	acc	ctg	gtc	acc	gtc	384	
Gln	Tyr	Tyr	Tyr	Met	Asp	Val	Trp	Gly	Arg	Gly	Thr	Leu	Val	Thr	Val		
			115				120					125					
tcg	agt	ggt	gga	ggc	ggt	tca	ggc	gga	ggt	ggc	agc	ggc	ggt	ggc	gga	432	
Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly		
		130				135					140						
tcg	tct	gag	ctg	act	cag	gac	cct	gct	gtg	tct	gtg	gcc	ttg	gga	cag	480	
Ser	Ser	Glu	Leu	Thr	Gln	Asp	Pro	Ala	Val	Ser	Val	Ala	Leu	Gly	Gln		
					150				155					160			
aca	gtc	agg	atc	aca	tgc	caa	gga	gac	agc	ctc	aga	agc	tat	tat	gca	528	
Thr	Val	Arg	Ile	Thr	Cys	Gln	Gly	Asp	Ser	Leu	Arg	Ser	Tyr	Tyr	Ala		
				165					170					175			
agc	tgg	tac	cag	cag	aag	cca	gga	cag	gcc	cct	gta	ctt	gtc	atc	tat	576	
Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr		
			180					185					190				
ggt	aaa	aac	aac	cgg	ccc	tca	ggg	atc	cca	gac	cga	ttc	tct	ggc	tcc	624	
Gly	Lys	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser		
		195					200					205					
agc	tca	gga	aac	aca	gct	tcc	ttg	acc	atc	act	ggg	gct	cag	gcg	gaa	672	
Ser	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Thr	Gly	Ala	Gln	Ala	Glu		
		210				215					220						
gat	gag	gct	gac	tat	tac	tgt	aac	tcc	cgg	gac	agc	agt	ggt	aac	cat	720	
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Asn	Ser	Arg	Asp	Ser	Ser	Gly	Asn	His		
		225			230				235					240			
gtg	gta	ttc	ggc	gga	ggg	acc	aag	ctg	acc	gtc	cta	ggt				759	
Val	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly					
			245					250									

<210> 205  
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 <212> DNA  
 <213> Artificial sequence

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(741)

&lt;223&gt; Polynucleotide encoding GMBC692 scFv protein

&lt;400&gt; 205

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1 5 10 15	
tcc ctt aga ctc tcc tgt gca gcc tct ggt ttc act ttc agt gac gcc	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala	
20 25 30	
tgg atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc	144
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca	192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala	
50 55 60	
ccc gtg aaa gac aga ttc acc atc tca cga gac gat tca aaa aac acg	240
Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctg tat ctg caa atg aac agt ctg aaa acc gag gac aca gcc ctg tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr	
85 90 95	
tac tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
agg gga acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga	384
Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
ggt ggc agc ggc ggt ggc gga tcg cag tct gtg ctg act cag cct gcc	432
Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala	
130 135 140	
tcc gtg tct ggg tct cct gga cag tcg atc acc atc tcc tgc act gga	480
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
acc agc agt gac gtt ggt ggt tat aac tat gtc tcc tgg tac caa caa	528
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg	576
His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg	
180 185 190	
ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg	624
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr	
195 200 205	
gcc tcc cta aca atc tct ggg ctc cag gct gag gac gag gct gat tat	672

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr  
 210 215 220

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ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gac tac gcc gca 192  
 Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Asp Tyr Ala Ala  
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ccc gtg aaa gac aga ttc acc atc tca cga gat gat tca aaa aac acg 240  
 Pro Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
 65 70 75 80

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 Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly  
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 115 120 125

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 180 185 190  
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 Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asp Thr  
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 Gly Trp Ile Asp Pro Ile Asn Ser Val Thr Asn Tyr Ala Gln Asn Phe  
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Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Gly	Ser		
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Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
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Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly		
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20 25 30	
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Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
ggc cgc atg aaa agc aag ggt agt ggt ggg aca aga gac tac gcc gca	192
Gly Arg Met Lys Ser Lys Gly Ser Gly Gly Thr Arg Asp Tyr Ala Ala	
50 55 60	
ccc gtg aat ggc aga ttc acc atc tca aga gat gat tca aaa aat acg	240
Pro Val Asn Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr	
65 70 75 80	
ctt tat ctg caa atg aac agc ctg aat acc gag gac aca ggc gta tat	288
Leu Tyr Leu Gln Met Asn Ser Leu Asn Thr Glu Asp Thr Gly Val Tyr	
85 90 95	
tat tgt acc tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly	
100 105 110	
agg ggc acc ctg gtc acc gtc tcg agt gga gga ggc ggt tca ggc gga	384
Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
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Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala	
130 135 140	
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Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
145 150 155 160	
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Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
165 170 175	
cac cca ggc aaa gcc ccc aaa ctc atg att tat gag ggc agt aag cgg	576
His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg	
180 185 190	
ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg	624



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tac tgc agc tca tat aca acc agg agc act cga gtt ttc ggc gga ggg      720
Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly
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ggc cgt att aaa agc aaa ggt agt ggt ggg aca ata gag tac gct gca      192
Gly Arg Ile Lys Ser Lys Gly Ser Gly Gly Thr Ile Glu Tyr Ala Ala
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ccc gtg aaa gac aga ttc atc atc tca cga gat gat tca aaa gac acg      240
Pro Val Lys Asp Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asp Thr
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ctg tat ctg caa atg gac agt ctg aaa acc gag gac aca gcc ctg tat      288
Leu Tyr Leu Gln Met Asp Ser Leu Lys Thr Glu Asp Thr Ala Leu Tyr
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tat tgt acg tgg gac tgg gat ttc tac tac ggt atg aac gtc tgg ggc      336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asn Val Trp Gly
    100                      105                      110

cag gga acc ctg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga      384
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
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ggg ggc agc ggc ggt ggc gga tcg tct gag ctg act cag gac cct gct      432

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Ser	Leu	Arg	Asn	Tyr	Tyr	Thr	Asn	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Gln		
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Pro	Asp	Arg	Phe	Ser	Gly	Ser	Ser	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr		
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atc	act	ggg	gct	cag	gcg	gaa	gat	gag	gct	gac	tat	tac	tgt	cat	tcc		672
Ile	Thr	Gly	Ala	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	His	Ser		
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Trp	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
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tat tgt acg tgg gac tgg gat ttc tac tac ggt atg gac gtc tgg ggg	336
Tyr Cys Thr Trp Asp Trp Asp Phe Tyr Tyr Gly Met Asp Val Trp Gly	
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aag ggg acc acg gtc acc gtc tcg agt ggt gga ggc ggt tca ggc gga	384
Lys Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly	
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Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala	
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Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly	
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Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln	
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His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg	
180 185 190	
ccc tca ggg gtt tct aat cgc ttc tct ggc tcc aag tct ggc aac acg	624
Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr	
195 200 205	
gcc tcc ctg aca atc tct ggg ctc cag gct gag gac gag gct gat tat	672
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35 40 45	
gga ggg atc atc cct atc tct gcc aca gca aac tac gca cag aag ttc	192
Gly Gly Ile Ile Pro Ile Ser Ala Thr Ala Asn Tyr Ala Gln Lys Phe	
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Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Met Ser Thr Ala Tyr	
65 70 75 80	
atg gaa ctg agc agc ctg aga tct gaa gac acg gcc gtg tat tac tgt	288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aga gat cgg gag ccc cac tac ttt gac aac tgg ggc cgg ggg aca	336
Ala Arg Asp Arg Glu Pro His Tyr Phe Asp Asn Trp Gly Arg Gly Thr	
100 105 110	
atg gtc acc gtc tgc agt gga ggc ggc ggt tca ggc gga ggt ggc tct	384
Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Ser	
115 120 125	
ggc ggt ggc gga agt gca ctg cct gtg ctg act cag cca ccc tgc gtg	432
Gly Gly Gly Gly Ser Ala Leu Pro Val Leu Thr Gln Pro Pro Ser Val	
130 135 140	
tct gaa gcc ccc agg cag ggg gtc acc atc tcc tgt tct gga agc agc	480
Ser Glu Ala Pro Arg Gln Gly Val Thr Ile Ser Cys Ser Gly Ser Ser	
145 150 155 160	
tcc aac atc gga aat aat gct gta agc tgg tac cag cag ctc cca gga	528
Ser Asn Ile Gly Asn Asn Ala Val Ser Trp Tyr Gln Gln Leu Pro Gly	
165 170 175	
cag gct ccc aaa ctc ctc atc tat tat gat gat ctg ctg ccc tca ggg	576
Gln Ala Pro Lys Leu Leu Ile Tyr Tyr Asp Asp Leu Leu Pro Ser Gly	
180 185 190	
gtc tct gac cga ttc tct gcc tcc aag tct ggc acc tca gcc tcc ctg	624
Val Ser Asp Arg Phe Ser Ala Ser Lys Ser Gly Thr Ser Ala Ser Leu	
195 200 205	
gcc atc agt ggg ctc cag tct gag gat gag gct gat tat tac tgt gca	672
Ala Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala	
210 215 220	
gca tgg gat gac agt ctg aat ggt gtg ata ttc ggc gga ggg acc cag	720
Ala Trp Asp Asp Ser Leu Asn Gly Val Ile Phe Gly Gly Gly Thr Gln	
225 230 235 240	
ctc acc gtt tta agt	735

Leu Thr Val Leu Ser  
245

<210> 213  
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<212> DNA  
<213> Artificial sequence

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<222> (1)..(780)  
<223> Polynucleotide encoding GMCC102 scFv protein

<400> 213

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tca gtg aag gtt tcc tgc aag gca cct gga tac acc ttc acc agc tac	96
Ser Val Lys Val Ser Cys Lys Ala Pro Gly Tyr Thr Phe Thr Ser Tyr	
20 25 30	
tat atg cac tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg	144
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	
35 40 45	
gga ata atc aac cct agt ggt ggt agc aca agc tac gca cag aag ttc	192
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe	
50 55 60	
cag ggc aga gtc acc atg acc agg gac acg tcc acg agc aca gtc tac	240
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr	
65 70 75 80	
atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt	288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aga ggt ggg gcc aga agc aat gat agt agt ggt tat tac aaa tca	336
Ala Arg Gly Gly Ala Arg Ser Asn Asp Ser Ser Gly Tyr Tyr Lys Ser	
100 105 110	
ccc ctc tcc tac tac tac ggt atg gac gtc tgg ggc cgg ggg aca atg	384
Pro Leu Ser Tyr Tyr Tyr Gly Met Asp Val Trp Gly Arg Gly Thr Met	
115 120 125	
gtc acc gtc tgc agt gga ggc ggc ggt tca ggc gga ggt ggc tct ggc	432
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly	
130 135 140	
ggt ggc gga agt gca cag tct gtg ctg act cag cca ccc tca gcg tct	480
Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser	
145 150 155 160	
ggg acc ccc ggg cag agg gtc acc atc tct tgt tct gga agc agc tcc	528
Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser	
165 170 175	
aac atc ggg agt aat act gta aac tgg tac cag cag ctc cca gga acg	576

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Asn Ile Gly Ser Asn Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr
      180                      185                      190

gcc ccc aaa ctc ctc atc tat agt aat aat cag cgg ccc tca ggg gtc      624
Ala Pro Lys Leu Leu Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val
      195                      200                      205

cct gac cga ttc tct ggc tcc aag tct ggc acc tca gcc tcc ctg gcc      672
Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala
      210                      215                      220

atc agt ggg ctc cag tct gag gat gag gct gat tat tac tgt gca gca      720
Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala
      225                      230                      235                      240

tgg gat gac agc ctg aat ggt gtg gta ttc ggc gga ggg acc aag gtc      768
Trp Asp Asp Ser Leu Asn Gly Val Val Phe Gly Gly Gly Thr Lys Val
      245                      250                      255

acc gtc cta ggt
Thr Val Leu Gly
      260

<210> 214
<211> 750
<212> DNA
<213> Artificial sequence

<220>
<221> CDS
<222> (1)..(750)
<223> Polynucleotide encoding GMCC105 scFv protein

<400> 214

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1                      5                      10                      15

tcc ctg aga ctc tcc tgc aca gcc tct gga ttc aac ctc ggt tcc cat      96
Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Asn Leu Gly Ser His
      20                      25                      30

ggc atg cac tgg gtc cgc cag gct ccc ggc aag ggg ctg gag tgg gtg      144
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35                      40                      45

gca gtt ata gga ttt gat gga acg act aaa tat tat gtg gac tcc gtg      192
Ala Val Ile Gly Phe Asp Gly Thr Thr Lys Tyr Tyr Val Asp Ser Val
      50                      55                      60

aag ggc cga ttc acc atc tcc agg gac aac tcc agg aac acc cta tct      240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Ser
      65                      70                      75                      80

ctg caa atg aac agc ctg aga gct gag gac acg gct gtc tat tac tgt      288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85                      90                      95

gtg aga gaa gat tac tac tat gat agt agt ggt tat tac ttt gac tac      336

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Val Arg Glu Asp Tyr Tyr Tyr Asp Ser Ser Gly Tyr Tyr Phe Asp Tyr  
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 Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
 115 120 125  
 ggc gga ggt ggc tct ggc ggt ggc gga agt gca ctt tct tct gag ctg 432  
 Gly Gly Gly Gly Ser Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu  
 130 135 140  
 act cag gac cct ttc gtg tct gtt gcc ttg gga cag aca gtc agg atc 480  
 Thr Gln Asp Pro Phe Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile  
 145 150 155 160  
 gca tgc cga gga gac agc ctc aga gat tct tat gca agt tgg tac cag 528  
 Ala Cys Arg Gly Asp Ser Leu Arg Asp Ser Tyr Ala Ser Trp Tyr Gln  
 165 170 175  
 cag aag cca gga cag gcc cct cga ctt ctc gtc tat gga aac aat ctt 576  
 Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Val Tyr Gly Asn Asn Leu  
 180 185 190  
 cgg ccc tcc ggg atc cct ggc cgg ttc tct ggc tcc agc tca gga gac 624  
 Arg Pro Ser Gly Ile Pro Gly Arg Phe Ser Gly Ser Ser Ser Gly Asp  
 195 200 205  
 aca gct tcc ttg tcc atc act gag act cag gcg gga gat gag gct gac 672  
 Thr Ala Ser Leu Ser Ile Thr Glu Thr Gln Ala Gly Asp Glu Ala Asp  
 210 215 220  
 tat tac tgc agt tcc cgg ggc aac agt acc tct cgc ctc tat gtc ttc 720  
 Tyr Tyr Cys Ser Ser Arg Gly Asn Ser Thr Ser Arg Leu Tyr Val Phe  
 225 230 235 240  
 gga act ggg acc aag ctg acc gtc cta ggt 750  
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 <223> Polynucleotide encoding GMCC106 scFv protein  
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 Thr Leu Ser Leu Thr Cys Ala Val Ser Val Gly Ser Ile Asn Glu Ser  
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 aac tgg tgg agt tgg gtt cgc cag tcc cca ggg aag gga ctg gag tgg 144  
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35 40 45	
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Ile Gly Glu Ile Tyr Pro Thr Gly Thr Thr Asn Tyr Asn Pro Ser Leu	
50 55 60	
gag agt cgg gtc acg ata tca gta gac aag tcc agg aac ctc ttc tcc	240
Glu Ser Arg Val Thr Ile Ser Val Asp Lys Ser Arg Asn Leu Phe Ser	
65 70 75 80	
ctg aaa ctg aag tct gtg acc gcc gcg gac tcg gcc atg tat ttc tgt	288
Leu Lys Leu Lys Ser Val Thr Ala Ala Asp Ser Ala Met Tyr Phe Cys	
85 90 95	
gcg aga gat cgg tgg gct ggt ggt ttt gat ctc tgg ggc aga ggg aca	336
Ala Arg Asp Arg Trp Ala Gly Gly Phe Asp Leu Trp Gly Arg Gly Thr	
100 105 110	
atg gtc acc gtc tcg agt gga ggc ggc ggt tca ggc gga ggt ggc tct	384
Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser	
115 120 125	
ggc ggt ggc gga agt gca cag tct gtg ttg acg cag ccg ccc tca gcg	432
Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Ala	
130 135 140	
tct ggg acc ccc ggg cag agg gtc acc atc tct tgt tct gga agc agc	480
Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser	
145 150 155 160	
tcc aac atc gga agt aat tct gta tac tgg tac cag cag ctc cca gga	528
Ser Asn Ile Gly Ser Asn Ser Val Tyr Trp Tyr Gln Gln Leu Pro Gly	
165 170 175	
acg gcc ccc aaa ctc ctc atc tat agg aat aat cag cgg ccc tca ggg	576
Thr Ala Pro Lys Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly	
180 185 190	
gtc cct gac cga ttc tct gct tcc aag tct ggc acc tca gcc tcc ctg	624
Val Pro Asp Arg Phe Ser Ala Ser Lys Ser Gly Thr Ser Ala Ser Leu	
195 200 205	
gcc atc agt ggg ctc cgg tcc gag gat gag gct gat tat tac tgt gca	672
Ala Ile Ser Gly Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala	
210 215 220	
gca tgg gat gac agc ctg agt ggt ctg gtc ttc ggc gga ggg acc aag	720
Ala Trp Asp Asp Ser Leu Ser Gly Leu Val Phe Gly Gly Gly Thr Lys	
225 230 235 240	
ctg acc gtc cta ggt	735
Leu Thr Val Leu Gly	
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<210> 216	
<211> 750	
<212> DNA	
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&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(750)

&lt;223&gt; Polynucleotide encoding GMCC107 scFv protein

&lt;400&gt; 216

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1 5 10 15	
tca gtg aag gtc tcc tgc agg acc tct gga tac acc ttc act gac cat	96
Ser Val Lys Val Ser Cys Arg Thr Ser Gly Tyr Thr Phe Thr Asp His	
20 25 30	
tct atg cat tgg gtg cgc cag gcc ccc gga cag agg ttt gag tgg atg	144
Ser Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Phe Glu Trp Met	
35 40 45	
gga tgg atc ggc gct gac agt ggt tcc aca cag tat tca cgg aac ttc	192
Gly Trp Ile Gly Ala Asp Ser Gly Ser Thr Gln Tyr Ser Arg Asn Phe	
50 55 60	
cag ggc aga ctc acc att ggc agg gac aca tcc gcg agc aca gtg tac	240
Gln Gly Arg Leu Thr Ile Gly Arg Asp Thr Ser Ala Ser Thr Val Tyr	
65 70 75 80	
atg gag ctg acc agt ctg aga tct gaa gac acg gct gtc tat tac tgt	288
Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aga gtg ggg gga ggt cag ggg tgg tac tcc ggc atg gac gtc tgg	336
Ala Arg Val Gly Gly Gly Gln Gly Trp Tyr Ser Gly Met Asp Val Trp	
100 105 110	
ggc aga ggc acc ctg gtc acc gtc tcg agt gga ggc ggc ggt tca ggc	384
Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly	
115 120 125	
gga ggt ggc tct ggc ggt ggc gga agt gca cag gct gtg ctg act cag	432
Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr Gln	
130 135 140	
ccg tcc tca gtg tct ggg gcc cca ggg cag agg gtc acc atc tcc tgc	480
Pro Ser Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys	
145 150 155 160	
act ggg agc agc tcc aac atc ggg gca agt tat gat gta cac tgg tac	528
Thr Gly Ser Ser Ser Asn Ile Gly Ala Ser Tyr Asp Val His Trp Tyr	
165 170 175	
cag cag ctt cca gga aca gcc ccc aaa ctc ctc atc tat aat aac aat	576
Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Asn Asn Asn	
180 185 190	
aat cgg ccc tca ggg gtc cct gac cga ttc tct ggc tcc agg tct ggc	624
Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Arg Ser Gly	
195 200 205	
acc tca gcc tcc ctg gcc atc act ggg ctc cag gct gag gat gag gct	672

Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala  
 210 215 220

gat tat tac tgc cac tcc tat gac agc aac ctg agt ggt gat gtc ttc 720  
 Asp Tyr Tyr Cys His Ser Tyr Asp Ser Asn Leu Ser Gly Asp Val Phe  
 225 230 235 240

gga tct ggg acc aag ctg acc gtc cta ggt 750  
 Gly Ser Gly Thr Lys Leu Thr Val Leu Gly  
 245 250

<210> 217  
 <211> 765  
 <212> DNA  
 <213> Artificial sequence

<220>  
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 <222> (1)..(765)  
 <223> Polynucleotide encoding GMCC108 scFv protein

<400> 217

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tca gtg acc gtt tcc tgc aag gct tct gga tac acc ttc att agt tac 96  
 Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile Ser Tyr  
 20 25 30

cac atg cac tgg gtt cga cag gcc cct gga caa ggg ctt gag tgg atg 144  
 His Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
 35 40 45

gga ata atc aat cct agt ggt ggt gac aca acc tac gca cag aag ttc 192  
 Gly Ile Ile Asn Pro Ser Gly Gly Asp Thr Thr Tyr Ala Gln Lys Phe  
 50 55 60

cag ggc aga gtc acc atg acc agg gac acg tca acg agc aca gtt tac 240  
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr  
 65 70 75 80

atg gag ctg agg agc ctg aga ttt gag gac acg gcc agg tat tac tgt 288  
 Met Glu Leu Arg Ser Leu Arg Phe Glu Asp Thr Ala Arg Tyr Tyr Cys  
 85 90 95

gcg aga gat cta aag ttc tac gat ttt cgg agt gga aag tat cag gac 336  
 Ala Arg Asp Leu Lys Phe Tyr Asp Phe Arg Ser Gly Lys Tyr Gln Asp  
 100 105 110

tac gga atg gat gtc tgg ggc cag gga acc ctg gtc acc gtc tcg agt 384  
 Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120 125

gga ggc ggc ggt tca ggc gga ggt ggc tct ggc ggt ggc gga agt gca 432  
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala  
 130 135 140

cag tct gtg ctg act cag cca ccg tcg ctg tca gtg gcc cca gga cag 480

Gln Ser Val Leu Thr Gln Pro Pro Ser Leu Ser Val Ala Pro Gly Gln  
145 150 155 160

acg gcc agt att acc tgt ggg gga aac gac att gga act aaa agt gta 528  
Thr Ala Ser Ile Thr Cys Gly Gly Asn Asp Ile Gly Thr Lys Ser Val  
165 170 175

cac tgg tac cag ctg aag cca ggc cag gcc cct gtg ttg gtc gtc tat 576  
His Trp Tyr Gln Leu Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr  
180 185 190

gat aat aga gac cgg ccc tca ggg atc cct gag cga ttc tct ggc tcc 624  
Asp Asn Arg Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
195 200 205

aac tct ggg aac acg gcc acc cta acc atc agc agg gtc gaa ggc ggg 672  
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Gly Gly  
210 215 220

gat gag gcc gac tat tat tgt cag gtg tgg gat agt agt att gat cat 720  
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ile Asp His  
225 230 235 240

tcc gaa tat gtc ttc gga act ggg acc aag ctg acc gtc cta ggt 765  
Ser Glu Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu Gly  
245 250 255

<210> 218  
<211> 732  
<212> DNA  
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<220>  
<221> CDS  
<222> (1)..(732)  
<223> Polynucleotide encoding GMCC109 scFv protein

<400> 218

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1 5 10 15

tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt agc agc tat 96  
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
20 25 30

gcc atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

tca gct att agt ggt agt ggt ggt agc aca tac tac gca gac tcc gtg 192  
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val  
50 55 60

aag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240  
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
65 70 75 80

ctg caa atg aac agc ctg aga gcc gag gac acg gcc gta tat tac tgt 288

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
                     85                    90                    95  
 gcg aaa agt caa tgg agt ggg agc tac tac ggc tca ttt gac tac tgg 336  
 Ala Lys Ser Gln Trp Ser Gly Ser Tyr Tyr Gly Ser Phe Asp Tyr Trp  
                     100                    105                    110  
 ggc cgg ggg aca atg gtc acc gtc tcg agt gga ggc ggc ggt tca ggc 384  
 Gly Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly  
                     115                    120                    125  
 gga ggt ggc tct ggc ggt ggc gga agt gca cag tct gtg ctg act cag 432  
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln  
                     130                    135                    140  
 cca ccc tca gtg tcc gtt tct cca gga cag aca gcc acc atc acc tgc 480  
 Pro Pro Ser Val Ser Val Pro Gly Gln Thr Ala Thr Ile Thr Cys  
                     145                    150                    155                    160  
 tct gga gac aaa ttg ggg gat aaa tat gtt tcc tgg tat cag aag aag 528  
 Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val Ser Trp Tyr Gln Lys Lys  
                     165                    170                    175  
 cca gga cag gcc cct gtg ctg gtc atc tat caa gat gac aag cgg ccg 576  
 Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gln Asp Asp Lys Arg Pro  
                     180                    185                    190  
 tca ggg atc cct gag cga ttc tct ggc tcc aac tct ggg aac aca gcc 624  
 Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala  
                     195                    200                    205  
 act ctg acc atc agc ggg acc cag gct atg gat gag ggt gac tat tac 672  
 Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Gly Asp Tyr Tyr  
                     210                    215                    220  
 tgt cag gcg tgg gac aga agt gtg ata ttc ggc gga ggg acc aag gtc 720  
 Cys Gln Ala Trp Asp Arg Ser Val Ile Phe Gly Gly Gly Thr Lys Val  
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 Thr Val Leu Gly  
  
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 <222> (1)..(750)  
 <223> Polynucleotide encoding GMCC110 scFv protein  
  
 <400> 219  
  
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                     1                    5                    10                    15  
 acc ctg tcc ctc acc tgc act gtc tct ggt gcc tcc atc agt agt gga 96

Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Ala	Ser	Ile	Ser	Ser	Gly		
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Gly	Tyr	Arg	Trp	Ile	Trp	Ile	Arg	Gln	His	Pro	Gly	Gln	Gly	Leu	Glu		
		35					40					45					
tgg	att	ggg	gac	atc	cat	tac	agt	ggg	agc	acc	cag	tac	aac	ccg	tcc	192	
Trp	Ile	Gly	Asp	Ile	His	Tyr	Ser	Gly	Ser	Thr	Gln	Tyr	Asn	Pro	Ser		
		50				55					60						
ctc	aag	agt	cga	gtt	gcc	ttg	aca	ctg	gac	agg	tct	aaa	aac	caa	ttc	240	
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Ser	Leu	Gln	Leu	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr			
				85				90					95				
tgt	gcg	aga	gat	ccg	cgt	gga	cac	acg	tat	ggt	tat	ggt	tac	tac	ttt	336	
Cys	Ala	Arg	Asp	Pro	Arg	Gly	His	Thr	Tyr	Gly	Tyr	Gly	Tyr	Tyr	Phe		
			100					105					110				
gac	tac	tgg	ggc	aaa	ggc	acc	ctg	gtc	acc	gtc	tcg	agt	gga	ggc	ggc	384	
Asp	Tyr	Trp	Gly	Lys	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly		
		115					120					125					
ggt	tca	ggc	gga	ggt	ggc	tct	ggc	ggt	ggc	gga	agt	gca	ctt	tct	tct	432	
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala	Leu	Ser	Ser		
		130				135					140						
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Glu	Leu	Thr	Gln	Asp	Pro	Asp	Val	Ser	Val	Ala	Leu	Gly	Gln	Thr	Val		
145					150					155					160		
acg	atc	aca	tgc	caa	gga	gac	aga	ctc	aga	aga	tat	tat	gca	agc	tgg	528	
Thr	Ile	Thr	Cys	Gln	Gly	Asp	Arg	Leu	Arg	Arg	Tyr	Tyr	Ala	Ser	Trp		
				165				170						175			
tac	cag	cag	aag	cca	gga	cag	gcc	cct	gtg	ctt	gtc	atc	ttt	cgt	aaa	576	
Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Phe	Arg	Lys		
			180					185					190				
aac	aac	cgg	ccc	tca	ggg	atc	cca	gac	cga	ttc	tct	ggc	tcc	agc	tca	624	
Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Ser	Ser		
		195					200					205					
gga	gac	aca	gct	tcc	ttg	acc	atc	act	ggg	gct	cag	gcg	gaa	gat	gag	672	
Gly	Asp	Thr	Ala	Ser	Leu	Thr	Ile	Thr	Gly	Ala	Gln	Ala	Glu	Asp	Glu		
		210				215					220						
gct	gac	tat	tac	tgt	aac	tca	cgg	gac	acc	agt	ggt	acc	ctt	tca	ttc	720	
Ala	Asp	Tyr	Tyr	Cys	Asn	Ser	Arg	Asp	Thr	Ser	Gly	Thr	Leu	Ser	Phe		
225					230					235					240		
ggc	gga	ggg	acc	cag	ctc	acc	gtt	tta	agt							750	
Gly	Gly	Gly	Thr	Gln	Leu	Thr	Val	Leu	Ser								
			245					250									

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 <213> Artificial sequence

<220>  
 <221> CDS  
 <222> (1)..(735)  
 <223> Polynucleotide encoding GMCC112 scFv protein

<400> 220

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Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1          5          10          15

tcc ctg aga ctc tcc tgt gca gcc tct gga ttc agc ttt agt act tat      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Thr Tyr
          20          25          30

gcc atg agt tgg gtc cgc cag gct cca ggg aag gga ctg gag tgg gtc      144
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45

tca ggc gtt agt gat ggt ggt gac aca ttc tac gca gac tcc gta agg      192
Ser Gly Val Ser Asp Gly Gly Asp Thr Phe Tyr Ala Asp Ser Val Arg
          50          55          60

ggc cgc ttc acc ctc tcc aga gac aac gcc aag aac acg ctg ttt ctg      240
Gly Arg Phe Thr Leu Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe Leu
          65          70          75          80

caa atg aac agc ctg aca gcc gag gac acg gcc aca tat tac tgt gcg      288
Gln Met Asn Ser Leu Thr Ala Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
          85          90          95

aaa gag ata gca aga att gga gtt cca aat ttc gac cac tgg ggc cag      336
Lys Glu Ile Ala Arg Ile Gly Val Pro Asn Phe Asp His Trp Gly Gln
          100          105          110

ggc acc ctg gtc acc gtc tcg agt gga ggc ggc ggt tca ggc gga ggt      384
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
          115          120          125

ggc tct ggc ggt ggc gga agt gca ctt gaa acg aca ctc acg cag tct      432
Gly Ser Gly Gly Gly Gly Ser Ala Leu Glu Thr Thr Leu Thr Gln Ser
          130          135          140

ccg ggc acc ttg tct ttg tct cca ggg gac aga gcc acc ctc tcc tgc      480
Pro Gly Thr Leu Ser Leu Ser Pro Gly Asp Arg Ala Thr Leu Ser Cys
          145          150          155          160

agg gcc agt cag agt att aga aat aac gac gtc gcc tgg tac cag cag      528
Arg Ala Ser Gln Ser Ile Arg Asn Asn Asp Val Ala Trp Tyr Gln Gln
          165          170          175

aaa cct ggc cag gca ccc aga ctc ctc atc tat agt gca tcc agg cgc      576
Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Ala Ser Arg Arg
          180          185          190

gcc act gac atc cca gac agg ttc agt ggc agt gcc tct ggg aca gac      624

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Ala Thr Asp Ile Pro Asp Arg Phe Ser Gly Ser Ala Ser Gly Thr Asp  
195 200 205

ttc act ctc acc atc agc aga ctg gag cct gag gat ttt gcg atg tac 672  
Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Met Tyr  
210 215 220

tac tgt cag cag tat ggc ggc tcg gcc tcc ttc ggc caa ggg aca cga 720  
Tyr Cys Gln Gln Tyr Gly Gly Ser Ala Ser Phe Gly Gln Gly Thr Arg  
225 230 235 240

ctg gag att aaa cgt 735  
Leu Glu Ile Lys Arg  
245

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<211> 750  
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<223> Polynucleotide encoding GMCC114 scFv protein

<400> 221

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tcg gtt aag gtc tcc tgc aag gct tct ggt gcc gcc gcc ttc agc agc 96  
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ala Ala Ala Phe Ser Ser  
20 25 30

tat gca atc agc tgg gtg cgt cag gcc cct gga cga ggg ctt gag tgg 144  
Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Glu Trp  
35 40 45

atg ggc ggc atc atc ccc atc tct gat aca cca aag tat gca cat aag 192  
Met Gly Gly Ile Ile Pro Ile Ser Asp Thr Pro Lys Tyr Ala His Lys  
50 55 60

ttc cag ggc aga gtc aca att acc gcg gac gaa tcc acg acc aca gtc 240  
Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Thr Thr Val  
65 70 75 80

ttc atg gag gtg agc ggc ctg aga tct gac gac acg gcc gtc tat tac 288  
Phe Met Glu Val Ser Gly Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr  
85 90 95

tgt gcg aca acc aca agg tat ggt tcg ggc act tat gat tac atg gac 336  
Cys Ala Thr Thr Arg Tyr Gly Ser Gly Thr Tyr Asp Tyr Met Asp  
100 105 110

gtc tgg ggc caa ggg aca atg gtc acc gtc tcg agt gga ggc ggc ggt 384  
Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly  
115 120 125

tca ggc gga ggt ggc tct ggc ggt ggc gga agt gca ctt tct tct gag 432

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu  
130 135 140

ctg act cag gac cct gct gtg tct gtg gcc ttg gga cag aca gtc agg 480  
Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg  
145 150 155 160

atc aca tgc caa gga gac agc ctc aga agt tat tat gca agt tgg tat 528  
Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr  
165 170 175

caa cag aag cca gga cag gcc ccg gta ctt gtc ttc tat ggt aaa aac 576  
Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Phe Tyr Gly Lys Asn  
180 185 190

aag cgg ccc tcg ggg atc cca gac cga ttc tcg ggc tcc acc tca gga 624  
Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Thr Ser Gly  
195 200 205

aac aca gct tcc ttg tcc atc acc ggg gct ctg gcg gat gat gag gcc 672  
Asn Thr Ala Ser Leu Ser Ile Thr Gly Ala Leu Ala Asp Asp Glu Ala  
210 215 220

gac tat tac tgt cac tcc cgt gac acc agt ggt gcc cag att ctt ttc 720  
Asp Tyr Tyr Cys His Ser Arg Asp Thr Ser Gly Ala Gln Ile Leu Phe  
225 230 235 240

ggc gga ggg acc aag ctg acc gtc cta ggt 750  
Gly Gly Gly Thr Lys Leu Thr Val Leu Gly  
245 250

<210> 222  
<211> 753  
<212> DNA  
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<220>  
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<222> (1)..(753)  
<223> Polynucleotide encoding GMCC118 scFv protein

<400> 222

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Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly  
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tca ctt aga ctc tcc tgt aca gcc tct gga ttc agt ttc act aac gcc 96  
Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Ser Phe Thr Asn Ala  
20 25 30

tgg atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtt 144  
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

ggc cgt att aaa agc aga aat gat ggt ggg gca aca gac tac gct gca 192  
Gly Arg Ile Lys Ser Arg Asn Asp Gly Gly Ala Thr Asp Tyr Ala Ala  
50 55 60

ccc gtg aaa ggc aga ttc acc atc tca aga gat gat tca aaa aac acg 240



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Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65          70          75          80

ttg tat ctg caa atg aat agc ctg aaa acc gac gac aca gcc gta tac      288
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Asp Asp Thr Ala Val Tyr
          85          90          95

tac tgt acc aca gat aac ttc cca tta cga ttt ttg gag tgg tta tcc      336
Tyr Cys Thr Thr Asp Asn Phe Pro Leu Arg Phe Leu Glu Trp Leu Ser
          100          105          110

cat cct gac tac tgg ggc caa ggg aca atg gtc acc gtc tcg agt gga      384
His Pro Asp Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
          115          120          125

ggc ggc ggt tca ggc gga ggt ggc tct ggc ggt ggc gga agt gca cag      432
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln
          130          135          140

gct gtg ctg act cag ccg tcc tca gtg tcc gtg tcc cca gga cag aca      480
Ala Val Leu Thr Gln Pro Ser Ser Val Ser Val Ser Pro Gly Gln Thr
          145          150          155          160

gtc acc atc acc tgc tct ggg gaa aaa ttg gac aat aaa tat att tcc      528
Val Thr Ile Thr Cys Ser Gly Glu Lys Leu Asp Asn Lys Tyr Ile Ser
          165          170          175

tgg tat caa cag agg cca ggc cgg tcc cct atc ctg gtc att tat caa      576
Trp Tyr Gln Gln Arg Pro Gly Arg Ser Pro Ile Leu Val Ile Tyr Gln
          180          185          190

gat cgg aag cgg ccc tca ggg atc cct gag cga ttc tct ggc tcc aac      624
Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn
          195          200          205

tcc ggg aac aca gcc act ctg acc atc acc ggg tcc cag cct ttg gat      672
Ser Gly Asn Thr Ala Thr Leu Thr Ile Thr Gly Ser Gln Pro Leu Asp
          210          215          220

gag gct gac tat tac tgt cag gcg tgg gac agc agc act gct tgg gag      720
Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Ala Trp Glu
          225          230          235          240

ttc ggc gga ggg acc aag ctg acc gtc cta ggt                          753
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
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<212> DNA
<213> Artificial sequence

<220>
<221> CDS
<222> (1)..(756)
<223> Polynucleotide encoding GMCC119 scFv protein

<400> 223

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tca gtg aag gtc tcc tgc aag gct tct aat tac acc ttc acc acc tac	96
Ser Val Lys Val Ser Cys Lys Ala Ser Asn Tyr Thr Phe Thr Thr Tyr	
20 25 30	
gac atc agc tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg	144
Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	
35 40 45	
gga tgg atc agc aca tat agt ggg aac aca aag tat gca cag aag ttc	192
Gly Trp Ile Ser Thr Tyr Ser Gly Asn Thr Lys Tyr Ala Gln Lys Phe	
50 55 60	
cag ggc aga gtc acc atg acc aga gac acg tcc acg agc gca gcc tac	240
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Ala Ala Tyr	
65 70 75 80	
atg gag ctg agg aac ctg aga tct gac gac acg gcc gtt tat ttc tgt	288
Met Glu Leu Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys	
85 90 95	
gcg aga gat atc cgt gtg tgg cgt ggt tcg ggc agt gtc cac tac ttc	336
Ala Arg Asp Ile Arg Val Trp Arg Gly Ser Gly Ser Val His Tyr Phe	
100 105 110	
gac ccc tgg ggg cga ggg acc acg gtc acc gtc tcg agt gga ggc ggc	384
Asp Pro Trp Gly Arg Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly	
115 120 125	
ggg tca ggc gga ggt ggc tct ggc ggt ggc gga agt gca caa tct gcc	432
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Ala	
130 135 140	
ctg act cag cct cgc tca gtg tcc ggg tct cct gga cag tca gtc acc	480
Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr	
145 150 155 160	
atc tcc tgc act gga acc agc aat gat gtt ggt ggt tat aac ttt gtc	528
Ile Ser Cys Thr Gly Thr Ser Ser Asn Asp Val Gly Gly Tyr Asn Phe Val	
165 170 175	
tcc tgg tac caa caa cac cca ggc aaa gcc ccc aaa ctc atg gtt tat	576
Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Val Tyr	
180 185 190	
aat gtc agt aag cgg ccc tca ggg gtc cct gat cgc ttc tct ggc tcc	624
Asn Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser	
195 200 205	
aag tct ggc aac acg gcc tcc ctg acc atc tct ggg ctc cag gct gag	672
Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu	
210 215 220	
gat gag gct gat tat tac tgc tcc tca tat gca cac agc tac acc ttg	720
Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala His Ser Tyr Thr Leu	
225 230 235 240	
gtc ttc ggc gga ggg acc aag gtc acc gtc cta ggt	756

Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly  
245 250

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<210> 224
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<212> DNA
<213> Artificial sequence
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<220>
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<222> (1)..(753)
<223> Polynucleotide encoding GMCC124 scFv protein
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20 25 30	
gct cta cat tgg gtg cgt cag gcc ccc gga caa agg cca gag tgg atg Ala Leu His Trp Val Arg Gln Ala Pro Gly Gln Arg Pro Glu Trp Met	144
35 40 45	
gca tgg atc aac act gcc aat gga aac aca aga tat tca caa aag ttc Ala Trp Ile Asn Thr Ala Asn Gly Asn Thr Arg Tyr Ser Gln Lys Phe	192
50 55 60	
cag ggc aga ctc acc att acc agg gac aca tcc gcg agc aca gcc ttc Gln Gly Arg Leu Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Phe	240
65 70 75 80	
atg gat ctg agc agc cta aga tct gag gac acg gct gta tat tac tgt Met Asp Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys	288
85 90 95	
gcg agg cag aaa gcc tac aag aat tac tac tac tac tac ggt atg gac Ala Arg Gln Lys Ala Tyr Lys Asn Tyr Tyr Tyr Tyr Tyr Gly Met Asp	336
100 105 110	
gtc tgg ggc caa ggc acc ctg gtc acc gtc tcg agt gga ggc ggc ggt Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly	384
115 120 125	
tca ggc gga ggt ggc tct ggc ggt ggc gga agt gca cag tct gtc gtg Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Val	432
130 135 140	
acg cag ccg ccc tca gtg tct gcg gcc cca gga cag aag gtc acc atc Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile	480
145 150 155 160	
tcc tgc tct gga agc agc tcc aac att ggg aat aat tat gta tcc tgg Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp	528
165 170 175	
tac caq caq ctc cca gga aca gcc ccc aaa ctc ctc atc tat gaa aat	576

Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Glu Asn  
 180 185 190  
 aat aag cga ccc tca gga att cct gac cga ttc tcg ggc tcc cag tct 624  
 Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gln Ser  
 195 200 205  
 ggc acg tca gcc acc ctg ggc atc tcc gga ctc cag act ggg gac gag 672  
 Gly Thr Ser Ala Thr Leu Gly Ile Ser Gly Leu Gln Thr Gly Asp Glu  
 210 215 220  
 gcc gat tat tac tgc gga aca tgg gat agc agc ctg cgt gct ggg gtg 720  
 Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu Arg Ala Gly Val  
 225 230 235 240  
 ttc ggc gga ggg acc aag ctg acc gtc cta ggt 753  
 Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly  
 245 250  
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 tcc ctg aga ctc tcc tgt gca gcc tct gga ttc agc ttc agt gac tac 96  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr  
 20 25 30  
 tcc atg cac tgg atc cgc cag gct cca ggg aag ggg ctg gag tgg ctt 144  
 Ser Met His Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu  
 35 40 45  
 tca cac att ggt aca agt act tct tac aca aac tac gca gat tct gtg 192  
 Ser His Ile Gly Thr Ser Thr Ser Tyr Thr Asn Tyr Ala Asp Ser Val  
 50 55 60  
 aag ggc cga ttc acc atc tcc aga gac aac gcc aag aac tct ttc tat 240  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Phe Tyr  
 65 70 75 80  
 ctc caa atg aac agc ctg aga gtc gac gac acg gct gtg tat ttc tgt 288  
 Leu Gln Met Asn Ser Leu Arg Val Asp Asp Thr Ala Val Tyr Phe Cys  
 85 90 95  
 gcg agg gga ttc ggg ggc ctc cgg ggc tac ttt gac tac tgg ggc cag 336  
 Ala Arg Gly Phe Gly Gly Leu Arg Gly Tyr Phe Asp Tyr Trp Gly Gln  
 100 105 110  
 ggc acc ctg gtc acc gtc tcg agt gga ggc ggc ggt tca ggc gga ggt 384

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 115 120 125  
 ggc tct ggc ggt ggc gga agt gca ctt tct tct gag ctg act cag gac 432  
 Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp  
 130 135 140  
 cct gct gtg tct gtg gcc ttg gga cag aca gtc aaa atc aca tgc caa 480  
 Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Lys Ile Thr Cys Gln  
 145 150 155 160  
 gga gac aga ctc cga aga ttt tat gca agc tgg tac cag cag aag cca 528  
 Gly Asp Arg Leu Arg Arg Phe Tyr Ala Ser Trp Tyr Gln Gln Lys Pro  
 165 170 175  
 ggc cag gcc cct cta ctt ctc atc tat ggt aaa aat agt cgg ccc tca 576  
 Gly Gln Ala Pro Leu Leu Leu Ile Tyr Gly Lys Asn Ser Arg Pro Ser  
 180 185 190  
 ggg atc ccg gac cga ttc tct ggc tcc acc tcg gga gcc aca gct tcc 624  
 Gly Ile Pro Asp Arg Phe Ser Gly Ser Thr Ser Gly Ala Thr Ala Ser  
 195 200 205  
 ttg acc atc act ggg gct cag gcg gaa gac gag gct gat tat tac tgt 672  
 Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys  
 210 215 220  
 aac tcc cgg gac agt tcc ggc agc ctc cat tct gtc ttc gga act ggg 720  
 Asn Ser Arg Asp Ser Ser Gly Ser Leu His Ser Val Phe Gly Thr Gly  
 225 230 235 240  
 acc aag gtc acc gtc cta ggt 741  
 Thr Lys Val Thr Val Leu Gly  
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 <222> (1)..(738)  
 <223> Polynucleotide encoding GMCC126 scFv protein  
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 acc ctg tcc ctc tcc tgc gct gtt tct ggt ttt tcc gtc acc agt ggt 96  
 Thr Leu Ser Leu Ser Cys Ala Val Ser Gly Phe Ser Val Thr Ser Gly  
 20 25 30  
 cac tac tgg ggc tgg atc cgg cag tcc cca ggg aag ggc ctg gag tgg 144  
 His Tyr Trp Gly Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp  
 35 40 45  
 att gga aat atc tat cat act ggg agc acc agg tac aat ccg tcc ctc 192

Ile	Gly	Asn	Ile	Tyr	His	Thr	Gly	Ser	Thr	Arg	Tyr	Asn	Pro	Ser	Leu	
50						55				60						
gag	agt	cga	gtc	tcc	atg	tca	gta	gac	acg	tcc	aag	aac	cag	ttc	tcc	240
Glu	Ser	Arg	Val	Ser	Met	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser	
65					70				75					80		
ctg	agg	ttg	act	tct	gtg	acc	gcc	gca	gac	acg	gcc	atc	tat	tat	tgt	288
Leu	Arg	Leu	Thr	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	
				85					90					95		
gcg	aga	gtg	ggc	cga	ggg	cag	cat	ctg	gta	cgg	ggg	gac	ttt	gac	tac	336
Ala	Arg	Val	Gly	Arg	Gly	Gln	His	Leu	Val	Arg	Gly	Asp	Phe	Asp	Tyr	
		100						105					110			
tgg	ggc	cga	ggc	acc	ctg	gtc	acc	gtc	tcg	agt	gga	ggc	ggc	ggg	tca	384
Trp	Gly	Arg	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	
		115					120					125				
ggc	gga	ggg	ggc	tct	ggc	ggg	ggc	gga	agt	gca	cag	tct	gtg	ctg	act	432
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala	Gln	Ser	Val	Leu	Thr	
		130				135					140					
cag	cca	ccc	tca	ata	tcc	gtg	tcc	cca	gga	cag	aca	gcc	agc	atc	acc	480
Gln	Pro	Pro	Ser	Ile	Ser	Val	Ser	Pro	Gly	Gln	Thr	Ala	Ser	Ile	Thr	
145					150					155					160	
tgc	tct	gga	gat	gaa	ttg	ggg	cat	aag	tat	gct	tcc	tgg	tat	cag	cag	528
Cys	Ser	Gly	Asp	Glu	Leu	Gly	His	Lys	Tyr	Ala	Ser	Trp	Tyr	Gln	Gln	
				165					170					175		
aag	cca	ggc	cag	tcc	cct	gtg	gtg	gtc	gtc	tat	caa	gat	aac	aag	cga	576
Lys	Pro	Gly	Gln	Ser	Pro	Val	Val	Val	Val	Tyr	Gln	Asp	Asn	Lys	Arg	
			180					185					190			
ccc	tca	ggg	atc	cct	gag	cga	ttc	tct	ggc	tcc	agt	tct	ggg	aac	aca	624
Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	Ser	Ser	Gly	Asn	Thr	
		195					200					205				
gcc	act	ctg	acc	atc	agc	ggg	acc	cag	gct	gtg	gat	gag	gct	gat	tat	672
Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Val	Asp	Glu	Ala	Asp	Tyr	
		210					215				220					
ttc	tgt	cag	gcg	tgg	gac	agc	agc	gct	gtg	gtc	ttc	ggc	gga	ggg	acc	720
Phe	Cys	Gln	Ala	Trp	Asp	Ser	Ser	Ala	Val	Val	Phe	Gly	Gly	Gly	Thr	
225					230					235					240	
aag	ctg	acc	gtc	cta	ggg											738
Lys	Leu	Thr	Val	Leu	Gly											
				245												

&lt;210&gt; 227

&lt;211&gt; 726

&lt;212&gt; DNA

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(726)

&lt;223&gt; Polynucleotide encoding GMCC127 scFv protein

&lt;400&gt; 227

cag gtc cag ctg gtg cag tct ggg gga ggt gtg gta cgg cct ggg ggg	48
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Arg Pro Gly Gly	
1 5 10 15	
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt gat gat tat	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr	
20 25 30	
ggc atg agc tgg gtc cgc caa gct cca ggg aag ggg ctg gag tgg gtc	144
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
tct ggt att aat tgg aat ggt ggt agc aca ggt tat gca gac tct gtg	192
Ser Gly Ile Asn Trp Asn Gly Gly Ser Thr Gly Tyr Ala Asp Ser Val	
50 55 60	
aag ggc cga ttc acc atc tcc aga gac aac gcc aag aac tcc ctg tat	240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr	
65 70 75 80	
ctg caa atg aac agt ctg aga gcc gag gac aca gcc gtg tat tac tgt	288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gca aga agg cgg tat gcg ttg gat tat tgg ggc cgg ggc acc ctg gtc	336
Ala Arg Arg Arg Tyr Ala Leu Asp Tyr Trp Gly Arg Gly Thr Leu Val	
100 105 110	
acc gtc tcg agt gga ggc ggc ggt tca ggc gga ggt ggc tct ggc ggt	384
Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly	
115 120 125	
ggc gga agt gca ctt tct tct gag ctg act cag gac cct gct gtg tct	432
Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser	
130 135 140	
gtg gcc ttg gga cag gca gtc agg atc aca tgc caa gga gac agt ctc	480
Val Ala Leu Gly Gln Ala Val Arg Ile Thr Cys Gln Gly Asp Ser Leu	
145 150 155 160	
aga acc aat tat gca agc tgg tac cag cag agg cca gga cag gcc cct	528
Arg Thr Asn Tyr Ala Ser Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro	
165 170 175	
gtt ctt gtc atc cgt ggt aac aac aac cgg ccc tca ggg atc cca gac	576
Val Leu Val Ile Arg Gly Asn Asn Asn Arg Pro Ser Gly Ile Pro Asp	
180 185 190	
cga ttc tct ggc tcc aac tca gga gac aca gtt tcc ctg acc atc act	624
Arg Phe Ser Gly Ser Asn Ser Gly Asp Thr Val Ser Leu Thr Ile Thr	
195 200 205	
ggg gct cag gcg gaa gat gag gct gac tat tat tgt aac tcc cgg gac	672
Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp	
210 215 220	
acc agt ggt tac cat tat gtc ttc gga act ggg acc aag ctg acc gtc	720

Thr Ser Gly Tyr His Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val  
 225 230 235 240

cta ggt 726  
 Leu Gly

<210> 228  
 <211> 738  
 <212> DNA  
 <213> Artificial sequence

<220>  
 <221> CDS  
 <222> (1)..(738)  
 <223> Polynucleotide encoding GMCC129 scFv protein

<400> 228

gag gtg cag ctg gtg gag acc ggg gga ggc ttg gca cag ccg ggg ggg 48  
 Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Ala Gln Pro Gly Gly  
 1 5 10 15

tcc ctg aga ctc tcc tgt gaa gcc tct gga ttc acc ttt aat aac tat 96  
 Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Asn Asn Tyr  
 20 25 30

gcc atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144  
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

tca ggt att agt att agt ggt tat agt aca ttc tac aca gac tcc gtg 192  
 Ser Gly Ile Ser Ile Ser Gly Tyr Ser Thr Phe Tyr Thr Asp Ser Val  
 50 55 60

cag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240  
 Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80

ttg caa atg aac agc ctg gga gtc gac gac acg gcc gta tat tac tgt 288  
 Leu Gln Met Asn Ser Leu Gly Val Asp Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

gcg aaa cgc cgt gga gag ggc ggc gac ttt gac tac tgg ggc cgg ggg 336  
 Ala Lys Arg Arg Gly Glu Gly Gly Asp Phe Asp Tyr Trp Gly Arg Gly  
 100 105 110

aca atg gtc acc gtc tcg agt gga ggc ggc ggt tca ggc gga ggt ggc 384  
 Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 115 120 125

tct ggc ggt ggc gga agt gca ctt tct tct gag ctg act cag gac cct 432  
 Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln Asp Pro  
 130 135 140

gct gtg tct gtg gcc ttg ggg cag aca gtc agg atc aca tgc caa gga 480  
 Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly  
 145 150 155 160

gac agc ctc aga ggc tat tat gca agc tgg tac caa cag aag gca gga 528



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Asp Ser Leu Arg Gly Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Ala Gly
      165                      170                      175

cag gcc cct gta ctt gtc atc tat ggt aag aac aac cgg ccc tca ggg      576
Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly
      180                      185                      190

atc cca gac cga ttc tct ggc tcc agc tca gga aac aca gct tcc ttg      624
Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser Leu
      195                      200                      205

acc atc act ggg gct cag gcg gaa gat gag gct gac tat tac tgt tac      672
Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr
      210                      215                      220

tcc cgg gac aga agt ggt aac cat cta gga atg ttc ggc gga ggg acc      720
Ser Arg Asp Arg Ser Gly Asn His Leu Gly Met Phe Gly Gly Gly Thr
      225                      230                      235                      240

aag gtc acc gtc cta ggt      738
Lys Val Thr Val Leu Gly
      245

<210> 229
<211> 744
<212> DNA
<213> Artificial sequence

<220>
<221> CDS
<222> (1)..(744)
<223> Polynucleotide encoding GMCC131 scFv protein

<400> 229

cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg gag      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1                      5                      10                      15

acc ctg tcc ctc acc tgc agt gtc tct ggt ggc tcc atc aga agt cat      96
Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Arg Ser His
      20                      25                      30

tac tgg agt tgg atg cgg caa ccc cca ggg aag gga ctg gag tgg att      144
Tyr Trp Ser Trp Met Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
      35                      40                      45

gga tac gtc tat tac act ggg agt acc aac tac aat ccg tcc ctc aag      192
Gly Tyr Val Tyr Tyr Thr Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
      50                      55                      60

agt cga gtc acc atg tca gta gac acg tcc aag aac cag ttc tcg ctg      240
Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
      65                      70                      75                      80

aac ctg agc tct gtg acc gct gcg gac acg gcc att tat tac tgt gcg      288
Asn Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Ile Tyr Tyr Cys Ala
      85                      90                      95

aga ttc cca tat agc agt ggc tcg aac ccg ctt gac tac tgg ggc cgg      336

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Arg Phe Pro Tyr Ser Ser Gly Ser Asn Pro Leu Asp Tyr Trp Gly Arg	
100 105 110	
gga acc ctg gtc acc gtc tcg agt gga ggc ggc ggt tca ggc gga ggt	384
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly	
115 120 125	
ggc tct ggc ggt ggc gga agt gca cag tct gtg ctg acg cag ccg ccc	432
Gly Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro	
130 135 140	
tca gtg tct gcg gcc cca gga cag agg gtc acc atc tcc tgc act ggg	480
Ser Val Ser Ala Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly	
145 150 155 160	
agc agc tcc aac atc ggg gca cgt tat gat gta cac tgg tac cag cac	528
Ser Ser Ser Asn Ile Gly Ala Arg Tyr Asp Val His Trp Tyr Gln His	
165 170 175	
ctg cca gga acc gcc ccc aaa ctc ctc atc tac ggt gac agc aat cga	576
Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asp Ser Asn Arg	
180 185 190	
ccc tca ggg gtc cct gac cga ttc tct ggt tcc aag tct ggc acc tca	624
Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser	
195 200 205	
gcc tcc ctg gcc atc act ggg ctc cag cct gag gat gag gct gat tat	672
Ala Ser Leu Ala Ile Thr Gly Leu Gln Pro Glu Asp Glu Ala Asp Tyr	
210 215 220	
tac tgc cag tcc tat gac agc agc ctg agt ggt gtg gta ttc ggc gga	720
Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Val Val Phe Gly Gly	
225 230 235 240	
ggg acc aag gtc acc gtc cta ggt	744
Gly Thr Lys Val Thr Val Leu Gly	
245	
<210> 230	
<211> 735	
<212> DNA	
<213> Artificial sequence	
<220>	
<221> CDS	
<222> (1)..(735)	
<223> Polynucleotide encoding GMCC136 scFv protein	
<400> 230	
gaa gtg cag ctg gtg cag tct ggg gga ggc ttg gta cag cct ggg ggg	48
Glu Val Gln Leu Val Gln Ser Gly Gly Leu Val Gln Pro Gly Gly	
1 5 10 15	
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt agc agc tat	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr	
20 25 30	
gcc atg agc tgg gtc cgc cag gct cca ggg aag ggg ctt gag tgg gtc	144

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
tca gct att agt ggt agt ggt ggt agc aca tac tcc gcc gac tcc gtg	192
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Ser Ala Asp Ser Val	
50 55 60	
aag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat	240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	
65 70 75 80	
ctg caa atg aac agc ctg aga gcc gag gac acg gcc gta tat tac tgt	288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gcg aaa tgc tgg cgt agt ggt acc agc tgc ccg gac ggc tgg ggc aaa	336
Ala Lys Cys Trp Arg Ser Gly Thr Ser Cys Pro Asp Gly Trp Gly Lys	
100 105 110	
ggg aca atg gtc acc gtc tgc agt gga ggc ggc ggt tca ggc gga ggt	384
Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly	
115 120 125	
ggc tct ggc ggt ggc gga agt gca ctt gaa att gtg ttg acg cag tct	432
Gly Ser Gly Gly Gly Gly Ser Ala Leu Glu Ile Val Leu Thr Gln Ser	
130 135 140	
cca gcc acc ctg tct gtg tct cca ggg gaa aga gcc acc ctc tcc tgc	480
Pro Ala Thr Leu Ser Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys	
145 150 155 160	
agg acc agt cag agt gtt ggc agc aag tta gcc tgg tac cag cag aaa	528
Arg Thr Ser Gln Ser Val Gly Ser Lys Leu Ala Trp Tyr Gln Gln Lys	
165 170 175	
cct ggc cag gct ccc agg ctc ctc atc tat gat gca tcc acc ggg gcc	576
Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Thr Gly Ala	
180 185 190	
act ggt gac cca gcc agg ttc agt ggc agt ggg tct ggg aca gag ttc	624
Thr Gly Asp Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe	
195 200 205	
act ctc acc atc agc aac ctg cag tct gaa gat ctt gca att tat tac	672
Thr Leu Thr Ile Ser Asn Leu Gln Ser Glu Asp Leu Ala Ile Tyr Tyr	
210 215 220	
tgt cag cag tat cat aag tgg ccg atc acc ttc ggc caa ggg aca cga	720
Cys Gln Gln Tyr His Lys Trp Pro Ile Thr Phe Gly Gln Gly Thr Arg	
225 230 235 240	
ctg gag att aaa cgt	735
Leu Glu Ile Lys Arg	
245	
<210> 231	
<211> 744	
<212> DNA	
<213> Artificial sequence	

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(744)

&lt;223&gt; Polynucleotide encoding GMCC138 scFv protein

&lt;400&gt; 231

gag gtg cag ctg gtg gag acc ggc cca gga ctg gtg aag ccc tca cag	48
Glu Val Gln Leu Val Glu Thr Gly Pro Gly Leu Val Lys Pro Ser Gln	
1 5 10 15	
acc cta tcc ctc acc tgc act gtg tct ggt ggc tcc atc agc agt ggt	96
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly	
20 25 30	
ggt tat tac tgg agc tgg atc cgc cag gtc cca ggg aag ggc ctg gag	144
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Val Pro Gly Lys Gly Leu Glu	
35 40 45	
tgg att ggg tac aac ttt tac aat ggg agc acg tac ttc aac ccg tcc	192
Trp Ile Gly Tyr Asn Phe Tyr Asn Gly Ser Thr Tyr Phe Asn Pro Ser	
50 55 60	
ctc aag agt cga gct acc ata tca att gac acg act aag aac cag ttc	240
Leu Lys Ser Arg Ala Thr Ile Ser Ile Asp Thr Thr Lys Asn Gln Phe	
65 70 75 80	
tcc ctg aag ttg agc tct gtg acc gcc gcg gac acg gcc gtc tat tat	288
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr	
85 90 95	
tgt gcg agg ggt aat gga tat agg tat ggt cgg tgg ttc gac ccc tgg	336
Cys Ala Arg Gly Asn Gly Tyr Arg Tyr Gly Arg Trp Phe Asp Pro Trp	
100 105 110	
ggc agg ggc acc ctg gtc acc gtc tcg agt gga ggc ggc ggt tca ggc	384
Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly	
115 120 125	
gga ggt ggc tct ggc ggt ggc gga agt gca ctt tcc tat gag ctg act	432
Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Tyr Glu Leu Thr	
130 135 140	
cag cca ccc tcg gtg tca gtg tcc cca gga cag acg gcc agg atc acc	480
Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Arg Ile Thr	
145 150 155 160	
tgc tct gga gat gca ttg cca aag caa tat gct tat tgg tac cag cag	528
Cys Ser Gly Asp Ala Leu Pro Lys Gln Tyr Ala Tyr Trp Tyr Gln Gln	
165 170 175	
aag cca ggc cag gcc cct gtg ctg gtg ata tct aaa gac agt gag agg	576
Lys Pro Gly Gln Ala Pro Val Leu Val Ile Ser Lys Asp Ser Glu Arg	
180 185 190	
ccc tca ggg atc cct gag cga ttc tct ggc tcc agc tca ggg aca aca	624
Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Ser Ser Gly Thr Thr	
195 200 205	
gtc acg ttg acc atc agt gga gtc cag gca gaa gac gag gct gac tat	672

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Val Thr Leu Thr Ile Ser Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr
 210                               215                               220

tac tgt caa tca gca gac agc agt ggt act tat tgg gtg ttc ggc gga      720
Tyr Cys Gln Ser Ala Asp Ser Ser Gly Thr Tyr Trp Val Phe Gly Gly
 225                               230                               235                               240

ggg acc aag gtc acc gtc cta ggt                                     744
Gly Thr Lys Val Thr Val Leu Gly
      245

<210> 232
<211> 738
<212> DNA
<213> Artificial sequence

<220>
<221> CDS
<222> (1)..(738)
<223> Polynucleotide encoding GMCC142 scFv protein

<400> 232

gag gtc cag ctg gtg cag tct gga gct gag gtg aag aag cct ggg gcc      48
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1                               5                               10                               15

tca gtg act att tcc tgc aag gca tct gga tac acc ttc acc gcc tac      96
Ser Val Thr Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ala Tyr
      20                               25                               30

tat ata tac tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg      144
Tyr Ile Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35                               40                               45

gga atg agc aac cct aat ggt ggt tac aca gtg tac cca ccg aat ttc      192
Gly Met Ser Asn Pro Asn Gly Gly Tyr Thr Val Tyr Pro Pro Asn Phe
 50                               55                               60

ctg ggc aga gtc acc acg acc ccg gac acg tca acg aac aca ata tat      240
Leu Gly Arg Val Thr Thr Thr Pro Asp Thr Ser Thr Asn Thr Ile Tyr
 65                               70                               75                               80

atg gag ctg aga agc ctg aga tct gaa gac acg gcc gtg tat tac tgt      288
Met Glu Leu Arg Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
      85                               90                               95

gcg aga ggt cgg ggg cgg gcc ccc agc aat gct ttt gac ttc tgg ggc      336
Ala Arg Gly Arg Gly Arg Ala Pro Ser Asn Ala Phe Asp Phe Trp Gly
      100                               105                               110

cga gga acc ctg gtc acc gtc tcg agt gga ggc ggc ggt tca ggc gga      384
Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
      115                               120                               125

ggt ggc tct ggc ggt ggc gga agt gca ctt tct tct gag ctg act cag      432
Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu Thr Gln
      130                               135                               140

gac cct gct gtg tct gtg gcc ttg gga cag aca gtc agg atc aca tgc      480

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Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys
145                      150                      155                      160

caa gga gac agc ctc aaa ttc tat tat gca agc tgg tat caa cag aag      528
Gln Gly Asp Ser Leu Lys Phe Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys
                      165                      170                      175

cca gga cag gcc cct gta ctt gtc ctc cat ggt aaa aat aac cgg ccc      576
Pro Gly Gln Ala Pro Val Leu Val Leu His Gly Lys Asn Asn Arg Pro
                      180                      185                      190

tca ggg atc cca gac cga ttc tct ggc tcc acc tca aga gac aca gct      624
Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Thr Ser Arg Asp Thr Ala
                      195                      200                      205

tcc ttg acc atc act ggg act cag gcg gaa gat gag gct gac tat tac      672
Ser Leu Thr Ile Thr Gly Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr
                      210                      215                      220

tgt aac tcc cgg gac aac agt gac aac att gtc ttc gga act ggg acc      720
Cys Asn Ser Arg Asp Asn Ser Asp Asn Ile Val Phe Gly Thr Gly Thr
225                      230                      235                      240

aag ctg acc gtc cta ggt
Lys Leu Thr Val Leu Gly
                      245

<210> 233
<211> 750
<212> DNA
<213> Artificial sequence

<220>
<221> CDS
<222> (1)..(750)
<223> Polynucleotide encoding GMCC151 scFv protein

<220>
<221> misc_feature
<222> (601)
<223> n equals a,t,g, or c

<400> 233

cag gtc cag ctg gtg cag tct ggg gga gga gtg gtc cag cct ggg agg      48
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1                      5                      10                      15

tcc ctg aga ctc tcc tgc aca gcc tct gga ttc aac ctc ggt tcc cat      96
Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Asn Leu Gly Ser His
20                      25                      30

ggc atg cac tgg gtc cgc cag gct ccc ggc aag ggg ctg gag tgg gtg      144
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35                      40                      45

gca gtt ata gga ttt gat gga acg act aaa tat tat gtg gac tcc gtg      192
Ala Val Ile Gly Phe Asp Gly Thr Thr Lys Tyr Tyr Val Asp Ser Val
50                      55                      60

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aag ggc cga ttc acc atc tcc agg gac aac tcc agg aac acc cta tct 240  
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Ser  
65 70 75 80  
  
ctg caa atg aac agc ctg aga gct gag gac acg gct gtc tat tac tgt 288  
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
  
gtg aga gaa gat tac tac tat gat agt agt ggt tat tac ttt gac tac 336  
Val Arg Glu Asp Tyr Tyr Tyr Asp Ser Ser Gly Tyr Tyr Phe Asp Tyr  
100 105 110  
  
tgg ggc cga gga acc ctg gtc acc gtc tcg agt gga ggc ggc ggt tca 384  
Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser  
115 120 125  
  
ggc gga ggt ggc tct ggc ggt ggc gga agt gca ctt tct tct gag ctg 432  
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Ser Glu Leu  
130 135 140  
  
act cag gac cct ttc gtg tct gtt gcc ttg gga cag aca gtc agg atc 480  
Thr Gln Asp Pro Phe Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile  
145 150 155 160  
  
gca tgc cga gga gac agc ctc aga gat tct tat gca agt tgg tac cag 528  
Ala Cys Arg Gly Asp Ser Leu Arg Asp Ser Tyr Ala Ser Trp Tyr Gln  
165 170 175  
  
cag aag cca gga cag gcc cct cga ctt ctc gtc tat gga aac aat ctt 576  
Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Val Tyr Gly Asn Asn Leu  
180 185 190  
  
cgg ccc tcc ggg atc cct ggc cgg ntc tct ggc ttc agc tca gga gac 624  
Arg Pro Ser Gly Ile Pro Gly Arg Xaa Ser Gly Phe Ser Ser Gly Asp  
195 200 205  
  
acc agt tcc ctg gcc atc act gag act cag gcg gga gat gag gct gac 672  
Thr Ser Ser Leu Ala Ile Thr Glu Thr Gln Ala Gly Asp Glu Ala Asp  
210 215 220  
  
tat tac tgc agt tcc cgg ggc aac agt acc tct cgc ctc tat gtc ttc 720  
Tyr Tyr Cys Ser Ser Arg Gly Asn Ser Thr Ser Arg Leu Tyr Val Phe  
225 230 235 240  
  
gga act ggg acc aag ctg acc gtc cta ggt 750  
Gly Thr Gly Thr Lys Leu Thr Val Leu Gly  
245 250

&lt;210&gt; 234

&lt;211&gt; 250

&lt;212&gt; PRT

&lt;213&gt; homo sapiens

&lt;400&gt; 234

Met Pro Ala Ser Ser Pro Phe Leu Leu Ala Pro Lys Gly Pro Pro Gly  
1 5 10 15

Asn Met Gly Gly Pro Val Arg Glu Pro Ala Leu Ser Val Ala Leu Trp  
20 25 30

Leu Ser Trp Gly Ala Ala Leu Gly Ala Val Ala Cys Ala Met Ala Leu  
                   35                                  40                                  45  
 Leu Thr Gln Gln Thr Glu Leu Gln Ser Leu Arg Arg Glu Val Ser Arg  
                   50                                  55                                  60  
 Leu Gln Gly Thr Gly Gly Pro Ser Gln Asn Gly Glu Gly Tyr Pro Trp  
                   65                                  70                                  75                                  80  
 Gln Ser Leu Pro Glu Gln Ser Ser Asp Ala Leu Glu Ala Trp Glu Asn  
                                   85                                  90                                  95  
 Gly Glu Arg Ser Arg Lys Arg Arg Ala Val Leu Thr Gln Lys Gln Lys  
                                   100                                  105                                  110  
 Lys Gln His Ser Val Leu His Leu Val Pro Ile Asn Ala Thr Ser Lys  
                                   115                                  120                                  125  
 Asp Asp Ser Asp Val Thr Glu Val Met Trp Gln Pro Ala Leu Arg Arg  
                   130                                  135                                  140  
 Gly Arg Gly Leu Gln Ala Gln Gly Tyr Gly Val Arg Ile Gln Asp Ala  
                   145                                  150                                  155                                  160  
 Gly Val Tyr Leu Leu Tyr Ser Gln Val Leu Phe Gln Asp Val Thr Phe  
                                   165                                  170                                  175  
 Thr Met Gly Gln Val Val Ser Arg Glu Gly Gln Gly Arg Gln Glu Thr  
                                   180                                  185                                  190  
 Leu Phe Arg Cys Ile Arg Ser Met Pro Ser His Pro Asp Arg Ala Tyr  
                                   195                                  200                                  205  
 Asn Ser Cys Tyr Ser Ala Gly Val Phe His Leu His Gln Gly Asp Ile  
                   210                                  215                                  220  
 Leu Ser Val Ile Ile Pro Arg Ala Arg Ala Lys Leu Asn Leu Ser Pro  
                   225                                  230                                  235                                  240  
 His Gly Thr Phe Leu Gly Phe Val Lys Leu  
                                   245                                  250